RANDOMISED TRIALS IN CHILD AND ADOLESCENT HEALTH IN DEVELOPING COUNTRIES

18th Edition
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Please send suggestions about this booklet to:

Prof Trevor Duke
University of Melbourne, Department of Paediatrics
Intensive Care Unit
Royal Children's Hospital
Parkville, 3052, Victoria, Australia
Email: **trevor.duke@rch.org.au**

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Introduction

Each year* this booklet is compiled to summarize the evidence on child and adolescent health derived from randomized or controlled trials in developing countries over the previous year. The aim is to make this information widely available to paediatricians, nurses, other health workers and administrators in resource poor settings where up-to-date information is hard to find. I hope that this information will be helpful in reviewing treatment policies, clinical practice, and public health strategies.

* Some readers have noted that I did not compile this book last year, it is true, the COVID-19 pandemic disrupted many things.

The method of searching for studies uses PubMed, a search engine that is freely available and widely used in countries throughout the world. The search strategy has been chosen to capture as many relevant studies as possible, although it is possible that I have missed some. If you know of a relevant RCT or meta-analysis that has not been included in this year's review, please let me know. The search strategy is reproducible by anyone with access to the Internet, through **http://www.ncbi.nlm.nih.gov/sites/entrez**

Randomized controlled trials (RCTs) are not the only valuable scientific evidence, and some RCTs, because of problems with design or implementation have limited value. However the method of the Randomized Trial is the Gold Standard for determining attributable benefit or harm from clinical and public health interventions. When done properly they eliminate bias and confounding. Their results should not be accepted uncritically but they should be evaluated for quality and validity. Before the result of an RCT can be generalized to another setting there must be consideration of wider applicability or reproducability, feasibility and potential for sustainability.

This year 450 trial publications were identified. This is an amazing research output in the midst of the pandemic, many studies of course were completed before the pandemic hit. These 450 trials were conducted in countries from all regions of the world. Many trials from 2020-21 will lead to significant changes in child health recommendations.

Where there were no trials this year under a certain sub-heading, I have left the heading in the book, to indicate the lack of trials. Many trials could be listed under several sub-headings, and there is overlap in the sub-headings, so there may be fewer gaps than is first apparent.

Most of the papers have free on-line access, which you can link to through the hyperlink in the title. Through HINARI (http://www.who.int/hinari/en/) a program set up by WHO in collaboration with publishers, the full-text versions of over 14,000 journal titles and 30,000 e-books are available to health institutions in over 100 countries. If your health institution (medical school, teaching hospital, nursing school, government office) has not registered with HINARI, you can check your eligibility and register online.

A brief summary of some of the important results in 2020-21

- Among over 4000 children with non-severe pneumonia in Pakistan, the incidence of treatment failure was 4.9% among placebo recipients and 2.6% with amoxicillin. Indicating a marginal benefit of amoxycillin, but also indicating that 95% of children recover from viral bronchiolitis / ALRI without antibiotics.

- In India, a small trial suggested zinc improved recovery from severe pneumonia, but a large meta-analysis of 11 trials showed no evidence that adjunctive zinc treatment improves recovery from pneumonia in children in low- and middled-income countries.

- Among adolescents affected by HIV in South Africa, social and economic equity, family cohesion, and social support from friends were protective factors from depression.

- A test message-based HIV prevention program improved HIV risk behaviour and testing among adolescents in Uganda.

- In Zambia there was a high rate of viral load failure in adolescents with HIV; 99 out of 273 participants receiving ART had virological failure. Among those with virological failure, resistance was highest to nucleoside reverse transcriptase inhibitors (81%), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (1.7%).

- Family based economic support improved ART adherence and viral load suppression among adolescents in Uganda.

- In India, supplemental feeding with guava resulted in higher haemoglobin, serum ferritin, vitamin C, and decreased prevalence of iron deficiency compared with children supplemented with banana or cucumber.

- In India, among children in intensive care who had stage 1-3 pressure areas, wound healing was faster with the use of medicated honey than with standard dressings.

- In a systematic review, among critically ill children on mechanical ventilators, chlorhexidine mouthwash or gel, reduced the incidence of developing ventilator-associated pneumonia (VAP).

- Mass distribution of azithromycin to preschool children twice yearly for 2 years has been shown to reduce childhood mortality in some high-mortality areas in sub-Saharan Africa. However mass distribution of azithromycin resulted in a large increase in macrolide resistance in gut bacteria found in children in Niger who received azithromycin: over 7 times the risk of macrolide resistance at 48 months, and cross-resistance to other antibiotic classes with increased beta-lactamase resistance also.

- A program to help Latina mothers manage stress in their children, showed improved emotion-coaching skills, and enabled them to more effectively encourage their children use coping strategies, to help them relax and calm down, improved ability to talk with their children about feelings, helping their children problem-solve, encouraging distraction, and helping their children improve their self-esteem.

- In 40 sites across South Africa violence against children was reduced by measures to improve parenting practices, improve caregiver mental health, increase caregiver alcohol/drug avoidance and improve family economic welfare.

- The pneumococcal conjugate vaccine (PCV) can reduce the risk of hospitalisation for children with pneumonia from cororaviruses (CoV), and pneumococcal coinfection may play a role in severe hospitalized CoV infections (before COVID-19). Among children without HIV, there was a 64.0% lower incidence of isolation of non-SARS Co-2 coronavirus in children with pneumonia among PCV9 recipients compared to placebo recipients.

- In Yogyakara in Indonesia, the infection of Aedes aegypti mosquitoes with the wMel strain of Wolbachia pipientis dengue virus infection reduced symptomatic dengue virus infection of any severity caused by any dengue virus serotype by 77%, and reduced hospitalisation from dengue virus infection by 86%.

- In studies vin Kenya, Uganda, Bangladesh and Brazil, parenting interventions delivered by trained community health volunteers in mother-child groups were effective in improving child development, including cognitive development, mother-infant attachment, and receptive language, and may reduce maternal depressive symptoms. In Rwanda, a parenting intervention focused on fathers reduced violence against their partner and harsh discipline towards children. However parenting interventions that focus only until 18 months of age did not have a sustained effect on child development at 6 years in Jamaica, suggesting that to have long term effectiveness there needs to be a sustained effect on the home environment.

- In India, for the treatment of diarrhoea without severe dehydration, cooked green banana reduced the duration of diarrhoea, and the risk of complications such as dehydration and persistent diarrhoea.

- In studies in China, use of probiotics (Bifidobacterium lactis and Lactobacillus acidophilus) reduced the duration of rotavirus (and other cause) acute diarrhoea and dehydration.

- In rural Ethiopia, supplying a bar of plain soap each month to households together with information promoting hand hygiene significantly decreased diarrheal episodes in children under 5 years old.

- In Indian children with drug-refractory epilepsy, a low glycaemic index diet (modified ketogenic) had an effect in reducing seizure frequency for half the children in the intervention arm, compared to children with no dietary intervention.

- In convulsive status epilepticus, levetiracetam was comparable to phenytoin, fosphenytoin and valproate in second-line therapy (after a short-acting benzodiazepine) for stopping seizures.

- In children with epilepsy due to a single cyst from neurocysticercosis, use of albendazole reduces seizure frequency.

- In rural Ghana, a liquid-petroleum gas stove and cylinder refills reduced air pollution exposure, including carbon monoxide exposure and particulate matter <2.5 μm (PM2.5), compared to children in households using biomass stove. And in Honduras a wood-burning stove with chimney (Justa stove) substantially lowered personal and kitchen particulate matter exposure, compared with traditional biomass cooking. In Nepal, LPG stoves reduced PM2.5 but had no effect on birth outcomes such as low birth weight.

- In South Africa, silver-impregnated ceramic water filters markedly reductions coliform bacteria in drinking water samples but had no effect on stunting. In Bangladesh it was found that contaminated soil, children's hands, food, and objects were the primary mechanisms of E. coli ingestion, so improving the water supply alone will be insufficient to reduce diarrhoea.

- In a multi-country study, voxelotor, an oral sickle haemoglobin polymerisation inhibitor given once a day led to in rapid and sustained improvements in haemoglobin and reduced sickling over a year of follow-up. In Nigeria, oral arginine reduced pain and spared the use of opioids and led to more rapid resolution of vaso-occlusive crises in children with Sickle cell disease.

- In South Africa, children with HIV despite effective viral suppressive antiretroviral therapy, can develop human immunodeficiency virus encephalopathy, as manifest by motor deficits such as spastic diplegia, language delays or impaired brain growth.

- In Cambodia, new dental caries were associated with detectable viral load in HIV affected children, and in Uganda, HIV exposed uninfected infants treated with lopinavir-ritonavir had less dental caries and gum disease at 6 years than those treated with lamivudine.

- In Kenya and Bangladesh, finished flooring (e.g. concrete) in houses rather than dirt was associated with reduced soil transmitted helminth infections, and in Nigeria a boardgame of “Worms and Ladders” with albendazole helped to reduce helminth reinfection rates and promote good hygiene practices among school-aged children.

- In China, use of tenofovir for pregnant women with Hepatitis B reduced the risk of HBV mother-to-child transmission after 6 months postpartum by 80%, and the infants had normal growth and neurodevelopment at 4 years of age.

- In a large systematic review, although the WHO integrated community case management of childhood illness program increased care seeking, there was no evidence of an effect on neonatal, infant or child mortality, without also strengthening health systems.

- In Kenya and Uganda in children who had recently been admitted with severe anaemia, 3 months of malaria chemoprevention with dihydroartemisinin-piperaquine (3-day courses at 2, 6, and 10 weeks) reduced readmission or death after hospital discharge. Similar effects were found in studies in Mali and Zambia. Intermittent preventative treatment seems to be highly effective for the duration of the treatment courses, but no longer effect was shown, suggesting the need to sustain intermittent malaria chemoprevention.

- In Mozambique, indoor residual spraying with pirimiphos-methyl reduced malaria vector exposures by 75% (indoors) and 68% (outdoors), in a region where there was high-transmission with pyrethroid resistant vectors (reducing the effect of pyrethroid-impregnated insecticide treated bed-nets).

- In 40 villages in Côte d'Ivoire, lethal house lures consisting of In2Care (Wageningen, Netherlands) Eave Tubes https://www.in2care.org/eave-tubes/, a small cylinder installed in the wall of a house with insecticide treated netting, reduced malaria case incidence by 40%, and with less exposure than indoor spraying.

- A systematic review of 11 trials in Uganda involving showed that compared to children with malaria treated with artemether-lumefantrine (AL), the PCR unadjusted treatment failure was significantly lower with dihydroartemisinin-piperaquine (DHA-PQ) at day 28 (RR 0.30, 95% CI 0.19-0.49) and at day 42 (RR 0.53, 95% CI 0.38-0.76). DHA-PQ appeared to reduce treatment failure and gametocyte carriage in Ugandan children.

- In a systematic review of the frequency of P. vivax infection after treatment of P. falciparum malaria to vary from 31.1% after artemether-lumefantrine, 14.1% after artesunate-amodiaquine, 7.4% (95% CI 6.7-8.1) after artesunate-mefloquine, and 4.5% (95% CI 3.9-5.3) after dihydroartemisinin-piperaquine.

- In a large observational study of over 25,000 children with malaria, of whom 8000 received a blood transfusion, transfusion was associated with improved survival when the admission haemoglobin concentration was up to 77 g/L (95% CI 65-110), and improved survival at haemoglobin concentrations up to 105 g/L (95% CI 71-115) if the child had impaired consciousness, and not associated with harm in children with a lactate >5mmol/L at any Hb threshold.

- In a trial in 10 villages in Guinea Bissau, food supplementation with a paste made of plant polyphenols, omega 3 fatty acids, highly fortified with micronutrients, and a high protein content, improved an index of working memory and cerebral blood flow (measured by near infra-red spectroscopy) in children younger than 4 years at risk of undernutrition.

- In Delhi, weight-for-age < -3 z-scores at 6 weeks of age was the best anthropomorphic index predicting death in the 6 weeks to 6 months of life, compared to weight-for-length < -3 and length-for-age < -3 and should be used to diagnose severe acute malnutrition and quantify risk in this age group.

- In rural Kenya, community-based health education groups for pregnant and postpartum women improved facility delivery, rates of exclusive breast feeding, contraceptive use and completion of infant immunisations.

- In India, antenatal administration of uterotonics such as oxytocin was associated with a substantially increased risk of intrapartum stillbirth and deaths on day 1 of life. This was shown in a case control study, within an RCT.

- In Nigeria, vaginal cleansing with 1% chlorhexidine gluconate solution before emergency caesarean section was effective in reducing rates of maternal infections.

- Among 2852 women at risk of preterm delivery in 29 hospitals in Bangladesh, India, Kenya, Nigeria, and Pakistan, intramuscular dexamethasone resulted in significantly lower risks of neonatal death alone and stillbirth or neonatal death than the use of placebo, without an increase in the incidence of possible maternal bacterial infection. And a systematic review of 27 studies involving over 11,000 women at risk of preterm birth found that treatment with antenatal corticosteroids reduces the risk of perinatal death, neonatal death and respiratory distress syndrome and probably reduces the risk of intraventricular haemorrhages.

- In a systematic review of 13 RCTs involving over 15,000 pregnant adolescents, multiple-micronutrient supplementation reduced low birth weight, preterm birth, and small-for-gestational-age births. In studies in Tanzania, pre-natal multiple micronutrient supplementation had no significant effect on weight gain in the first 6 months of life.

- In Cambodia where infant beri beri is common, maternal thiamine dose (10 mg/day) improved infants' language development but did not affect motor or visual development.

- In an 11-15 year follow up of infants in a micronutrient trial, duration gestation and birthweight were positively associated with adolescent neurodevelopment in Tanzania, that is low birthweight (<2500 grams) was associated with lower intelligence and executive function scores.

- In Brazil, the Primeiros Laços, a nurse home visiting program for adolescent mothers living in an urban deprived urban area improved measures of parental well-being and the maternal parenting behaviour.

- In India, for children with acute pyogenic meningitis in children aged 3 months to 14 years who have rapid initial recovery, outcomes at 30 and 90 days (treatment failure, hearing impairment, hydrocephalus, other neurological sequelae), were no different with 7 or 10 days of ceftriaxone.

- In primary health care centres in Lagos, Nigeria, SMS text message reminders to mothers or caregivers 2 days before scheduled vaccines resulted in an increase in return for immunisation, but similar messages were not effective in increasing follow-up rates for family planning or antenatal care. In another trial in Ethiopia, a similar positive effect on all vaccine uptake was found following SMS text message reminders. Text message reminders can be effective in increasing coverage of the routine immunization program and timely receipt of vaccines in resource-limited settings.

- In India, children aged 6-12 years with spastic quadriplegic cerebral palsy with Gross Motor Function Classification System of levels III and IV who participated in a training program lasting for one hour for 4 days per week for 6 weeks of strength training called dynamic surface exercise training had significant improvements in trunk control and measures of gross motor function.

- In Uganda, among 1416 newborns in the community, the prevalence of hypoglycaemia (blood glucose concentration of < 47 mg/dl – 2.6mmol/L) was 2.2%. The risk factors for neonatal hypoglycemia were delayed breastfeeding initiation and age of 3 days or less.

- In Zambia, within a chlorhexidine cord care trial, mothers were provided with clean delivery kits, containing soap, gloves, cord clamps, plastic sheet, razor blade, matches, and candle. A reduction in risk of early newborn death (1-6 days) was associated with use of gloves, plastic sheets for clean delivery, and razor blades and cord clamps for cord care.

- Among intrauterine growth restricted newborns in India, delayed cord clamping increased superior vena cava blood flow, right ventricular output, superior mesenteric artery blood flow velocity, haematocrit, and serum ferritin, but did not result in an increased need for phototherapy, compared with early cord clamping. In 2 studies in India, umbilical cord milking increased the haematocrit to a similar level as delayed cord clamping in vigorous newborns at or near term.

- WHOs 4 Essential Elements of Newborn Care are: immediate and thorough drying, skin to skin contact, delayed cord clamping, and early initiation of breastfeeding. In Nepal, among over 28,000 mother-infant pairs, skin to skin contact (adjusted hazard ratio = 0.64 [0.51, 0.81]) and early initiation of breastfeeding (aHR = 0.72 [0.60, 0.87]) were associated with lower risk of neonatal mortality.

- In a large systematic review of 9 RCTs on the effect of gastric lavage involving 3688 newborns with meconium aspiration, 9 randomized controlled trials, there was a a significant reduction in the incidence of feeding intolerance (relative risk 0.70; 95% confidence interval 0.58,0.85) after gastric lavage.

- In Ghana, India, Malawi, Nigeria, and Tanzania among infants with a birth weight 1-1.8 kg immediate kangaroo mother care resulted in lower mortality at 28 days than conventional care with kangaroo mother care initiated after stabilization.

- In India, among hemodynamically stable preterm very-low-birth-weight (VLBW) neonates, early enteral nutrition (80 mL/kg/d) started on day 1 of life with the rapid advancement of feeds (20 mL/kg/d) enabled an earlier achievement of full feeds (180 mL/kg/d) at median of day 6. A similar trial in Bangladesh also showed early enteral feeding found to be safe and beneficial in reducing the time to reach full enteral feeding and better weight gain in growth restricted preterm infants.

- A systematic review of RCTs on feeding volume in preterm newborns showed that high volume feeds (≥ 180 mL/kg/day of fortified human milk or preterm formula, or ≥ 200 mL/kg/day of unfortified human milk or term formula improves weight gain during hospital stay, but no evidence of an effect on linear growth or head circumference.

- A meta-analysis of trials of probiotics in preterm newborns showed they were associated with significantly reduced necrotising enterocolitis (30 studies, n = 77,018; OR: 0.60; 95% CI: 0.50, 0.73; P <0.00001), reduced length of hospital stay (21 studies, n = 65,858; OR: 0.85; 95% CI: 0.74, 0.97), and reduced all-cause mortality (27 non-RCTs, n = 70,977; OR: 0.77; 95% CI: 0.68, 0.88).

- In India, a RCT of caffeine for apnoea in preterm newborns showed caffeine could be stopped safely at 33-34 weeks when 7 days apnoea-free.

- In term newborns in India with hypoxic-ischaemic encephalopathy, therapeutic hypothermia reduced mortality and neurological abnormalities, and resulted in more normal survivors at 18 months of age.

- A RCT of music therapy for painful procedures among over 3000 newborns in a neonatal intensive care unit in India showed that those who received music therapy had reduced hospital stay, oxygen dependency, incidences of apnoea, pain during procedures and better neurodevelopmental outcome.

- Three systematic reviews of the use of levetiracetam in neonatal seizures suggested it is not more effective than phenobarbital, likely similar, but levetiracetam was associated with a lower risk of adverse events than phenobarbitone.

- In the treatment of neonatal infections where extended-spectrum beta-lactamase strains of enteric Gram-negative bacteria are common, effective antibiotics are expensive and scarce. Fosfamycin is an old antibiotic that may be useful. In Malawi, the combination of amikacin and fosfomycin (100 mg/kg IV 12 hourly for 48 hours) enhanced bactericidal activity and prevented the emergence of resistance in invitro studies and was effective clinically in a small RCT of neonatal sepsis.

- In India, for newborns with culture-positive sepsis who have reached clinical and microbiologic remission at day 7, 10 days of antibiotic therapy was as effective as 14 days.

- In a cluster RCT in 22 schools in India, multiple micronutrient powder in preschool meals reduced anaemia and iron deficiency, and some aspects of child development (expressive language), but micronutrients without other components of nurturing care will have a limited effect on development.

- A systematic review of 10 trials, involving 3319 children older than 2 years in Bangladesh, Brazil, India, Kuwait, Philippines, South Africa, and Sri Lanka, showed that fortification of wheat flour with iron reduced anaemia.

- In 870 children 6-23 months in Pakistan, 50 grams/day of a lipid-based nutrient supplement significantly reduced the risk of stunting (RR = 0.91, 95% CI; 0.88-0.94, $p<0.001$) and wasting (RR = 0.78, 95% CI; 0.67-0.92, $p = 0.004$) as compared to children who received the standard government health services.

- In rural Kenya, in a cluster RCT, maternal, infant, and young child nutrition counselling, support from trained community health volunteers, health professionals and community and mother support groups lead to improved rates and prolonged exclusive breast feeding (81.7%) at 6 months, compared to breast feeding rates in clusters with no additional community intervention (42.2%) $p=0.001$.

- Over one year in 15 schools with 779 schoolchildren (aged 8-12) and their caregivers in Nepal, school gardens led to increases in healthy food knowledge and behaviour among children and their caregivers, including a liking for vegetables, agricultural knowledge, and home garden productivity.

- In India, among 48 children with acute leukaemia, oral glutamine (400 mg/kg body weight per day) reduced oral mucositis to 4% in 24 children given glutamine compared to 63% in 24 given placebo. In another trial, ketamine 1 mg/kg oral rinse did not significantly reduce oral mucosal pain.

- In 48 Ethiopian communities, antibiotic treatments of infected pre-school children did not result in significantly less ocular chlamydia infections (13%) than communities in which there was mass distribution (5%).

- In Tanzania, 639 children with Schistosoma mansoni infection were treated with praziquantel alone or praziquantel plus Dihydroartemisinin-piperaquine (DHP) combination. At 3 weeks post-treatment, cure rates were 88% (263/298, 95% CI = 84.1%-91.4%) and 81% (277/341, 95% CI = 76.7%- 85.0%) for the combination therapy and praziquantel alone, respectively ($p < 0.01$, odds ratio (OR) = 1.74, 95% CI of OR = 1.11 to 2.69). At 8 weeks, cure rates were higher in the praziquantel-DHP combination group 82% (244/298, 95% CI = 77.1%- 85.8%), compared to 64% (218/341, 95% CI = 58.7%-68.8%) in those treated with praziquantel alone ($p < 0.0001$, OR = 2.55, 95%CI of OR = 1.75 to 3.69). Praziquantel alone is insufficient for the treatment of schistosomiasis, partly due to its poor efficacy against the juvenile worms. Artemisinin derivatives (such as DHP) are effective against juvenile worms but are less effective against adult worms. In South Africa a trial of 2 doses of praziquantel (40mg / kg and 60mg / kg) showed no increased benefit on cure rate for Schistosomiasis using the higher dose at 4 weeks of 79% (40mg/kg) and 83% (60mg/kg), but increased side effects with the higher dose.

- In 40 schools in Pakistan, a play-based life-skills intervention involving a biweekly structured game led by a coach followed by critical reflection and discussion for 30 minutes significantly reduced peer violence victimization, violence perpetration, and depression.

- In India, a bedside score for prediction of mortality in sepsis was trialled in 60 children, and accurately predicted outcome (AUC 91%). The score, aiming to identify children with refractory septic shock, is based on blood lactate (1 point if above 8 mmol/L or increased > 1 mmol/L after 6 h of management), a vasoactive-inotrope score (1 point), and the presence of a severe cardiomyopathy defined by a cardiac index < 2.2L/min.m2 or a left ventricle ejection fraction < 25% (3 points).

- In a meta-analysis of 28 studies, active community-based case-finding for tuberculosis increased the number of cases of tuberculosis notified in populations with risk factors for tuberculosis. Active community-based case finding for TB could change tuberculosis epidemiology in endemic settings.

- Within a large RCT, the use of a new diagnostic test GeneXpert MTB/RIF Ultra (Xpert Ultra) was more sensitive against a composite microbiological reference than the standard GeneXpert test: 72% (58 to 84%) for Xpert Ultra and 32% (20 to 47%) for Xpert.

- In rural Nigeria, a “scared-straight” campaign, using flip-charts with descriptions of tetanus disease severity had a negative effect; fewer women came for tetanus immunisation even though it increased their perceived risk of disease and their fear level.

- In Guinea Bissau, perfluoroalkyl substances, a group of widely used persistent environmental chemicals in household and industrial products but also present in soil, air, water, were found in serum of children. The presence of perfluoroalkyl in serum was associated with reduced measles antibody responses following measles vaccine.

- In a neonatal unit in Uganda an RCT of BCG vaccine, involving 560 newborns of any weight and gestation, with BCG given at birth or delayed for 6 weeks, showed that infectious disease incidence was lower in infants in the BCG at birth group than in the delayed group (98 presentations in the BCG at birth group vs 129 in the delayed BCG group; hazard ratio [HR] 0·71 [95% CI 0·53-0·95], p=0·023). BCG vaccination protects against non-tuberculous infectious disease during the neonatal period, as well as protecting against TB.

- A long term follow-up of children who received the killed-cell cholera vaccine in Bangladesh showed that protection is shorter-lived in children vaccinated before the age of 5 years (24% protection at 4 years post-vaccination) than in people vaccinated at the age of 5 years or older (49% protection at 4 years). Vaccine protection drops notably after 3 years in children vaccinated at 1-4 years of age.

- The malaria vaccine R21 with adjuvant matrix-M (R21/MM) was tested in children in Burkina Faso. Vaccinated children developed high titres of malaria-specific anti-Asn-Ala-Asn-Pro (NANP) antibodies 28 days after the third vaccination, and the protective efficacy against clinical malaria was above 70% at 6 and 12 months. Antibody titres waned but were boosted to levels like peak titres after the primary series of vaccinations, after a fourth dose administered 1 year later.

- In Vietnam, in a trial of 10-valent pneumococcal conjugate vaccine involving 1201 infants, a two-dose primary vaccination series was non-inferior to a three-dose primary vaccination series while two doses given with a wider interval between doses increased immunogenicity. And in South Africa, for both PCV13 and PCV10, a 1+1 dosing schedule (first dose at either 6 or 14 weeks with second dose at 40 weeks) was non-inferior to a 2 + 1 schedule (2 priming doses at 6 and 14 plus booster at 40 weeks).

- A trial of PCV-10 and the 23-valent polysaccharide pneumococcal vaccine (PPV-23) in Brazil in pregnant HIV positive women showed the vaccines were equally safe and immunogenic in pregnant women with HIV and conferred similar levels of seroprotection to their infants, although PPV-23 will cover a broader range of pneumococcal serotypes.

- In Nigeria, to assess the immunogenicity of the new polio vaccine schedule bOPV + IPV immunization schedule, found that a schedule giving 2 IPV doses: bOPV at birth, 6 and 10 weeks, bOPV+IPV at week 14 and IPV at week 18, achieved excellent immunogenicity (>98%) to polio virus 1 and 2, and if a second dose of IPV was given, (week 14 and 18) also excellent immunogenicity to poliovirus type 2. But one dose of IPV was not enough, achieving only 72% immunogenicity to polio virus type 2. Similar results were found in a study in China.

- In a population of severely ill children with pneumonia in Egypt, the baseline rate of vitamin D deficiency was over 30%, and vitamin D supplementation (a single injection of

1 mL of 100,000 IU of vitamin D3) resulted in more rapid resolution of pneumonia severity than placebo. And a meta-analysis of 46 controlled trials showed that vitamin D supplementation had a small preventative effect against the development of acute respiratory infection. A trial in India showed no effect of vitamin D on the treatment of asthma, and a meta-analysis did not show an effect of oral vitamin D supplementation on linear growth or stunting.

- A meta-analysis of 3 trials involving 345 preterm infants showed that enteral zinc supplementation in preterm infants may decrease all-cause mortality (RR 0.55, 95% CI 0.31 to 0.97.

Again, this year some studies had small sample sizes, and many of the results should be considered preliminary. The terms or phrases: 'no difference', non-inferiority, and equivalence were used in some papers with insufficient consideration to the possibility of a type II error. This can be misleading and may result in the discarding of an effective intervention, or numerous inadequate trials of the same intervention.

I have been liberal in what is included as an RCT. Many papers are the reports of sub-studies within an RCT, they may be cohort or background studies rather than the primary results of the completed RCT.

Randomised trials often report the "average effect", that is, the effect on the overall population. However, depending on how specifically that population is defined, within that population may be children who will benefit from the therapy or intervention, children for whom the therapy will have no effect, and some children for whom it may be harmful. The "average" of these effects may be "no overall effect", but it is increasingly important that researchers try to understand the effects for individuals or sub-groups within trials, and the context in which benefit or not occurs.

Some of the context differences that influence the results of a trial include: individual or population characteristics, comorbidities, the health care environment and health care providers, geographical factors, other interventions, the delivery mechanism for the drug, vaccine or other intervention, the disease stage and specific aetiology, economic, social and cultural characteristics of the population and individuals within it…and other unknown factors. This can be even more complex in understanding systematic reviews of randomised trials, where heterogeneity is often incompletely reported, and where there will be heterogeneity *within and between* studies.

Incorporating an understanding of the observed effect in context requires a nuanced approach, and the randomised trial design is not always the best method to trial all interventions. This can be the case for complex interventions (i.e. a complex clinical therapy or a health system improvement program) where other methods of evaluation may be more useful.

Since 2002 there have been **3542 trial publications** summarised in the 18 editions of this book. It is interesting to see the evolution of trials each year. It is encouraging to see the

evaluation of the developmental, psychological, and mental health effects of interventions. Also encouraging is the increased number of trials that include adolescents; particularly this year trials of interventions to reduce violence against adolescents and mothers, increase retention in chronic disease programs, and improve school retention and self-esteem.

Please feel free to distribute this booklet to your colleagues. The previous editions (2002-2018) are available.

In the past year, countless paediatricians, nurses and other health care workers throughout the world have selflessly dedicated themselves to the fight against COVID-19, many have become gravely ill and too many have died. To these courageous people I humbly dedicate this edition.

Trevor Duke
July 2021

Search strategy

Pubmed Advanced strategy, search: ("Developing Countries"[Mesh] OR (austere OR limited resource* OR "resource limited" OR low resource* OR transitioning econom* OR lami countr* OR transitional countr* OR "low gdp" OR "low gnp" OR "low gross domestic" OR "low gross national" OR ((emerging OR developing OR "low income" OR "middle income" OR (low AND middle) OR underdeveloped OR "under developed" OR under-developed OR underserved OR "under served" OR under-served OR (less-developed) OR deprived OR poor) AND (countr* OR nation* OR econom* OR population OR world)) OR "third world" OR LMIC OR LMICs) OR "Africa"[Mesh] OR "caribbean region"[Mesh] OR "central america"[Mesh] OR "latin america"[Mesh] OR "mexico"[Mesh] OR "south america"[Mesh] OR "europe, eastern"[Mesh] OR "indian ocean islands"[Mesh] OR "pacific islands"[Mesh] OR "New Guinea"[Mesh] OR India OR Africa OR Asia OR South-America OR Papua-New-Guinea OR Pacific) AND (newborn* OR new-born* OR baby OR babies OR neonat* OR neo-nat* OR infan* OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric* OR paediatric* OR adolescen* OR youth OR youths OR teen OR teens OR teenage*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized-controlled-trial*[tiab] OR randomised-controlled-trial*[tiab] OR randomized-trial*[tiab] OR randomised-trial*[tiab] NOT (animals[mh] NOT humans[mh])): Publication date between July 1 2020 and June 30 2021.

Acute respiratory infection

(See also: Zinc; Vaccines - Pneumococcal vaccine; Hygiene and environmental health)

Prevention of pneumonia

(see Vaccines – Pneumococcal)

Treatment of pneumonia

N Engl J Med. 2020 Jul 2;383(1):24-34.
doi: 10.1056/NEJMoa1911998.

Randomized Trial of Amoxicillin for Pneumonia in Pakistan

Fyezah Jehan[1], Imran Nisar[1], Salima Kerai[1], Benazir Balouch[1], Nick Brown[1], Najeeb Rahman[1], Arjumand Rizvi[1], Yasir Shafiq[1], Anita K M Zaidi[1]

Abstract

Background: The World Health Organization (WHO) recommends oral amoxicillin for patients who have pneumonia with tachypnea, yet trial data indicate that not using amoxicillin to treat this condition may be noninferior to using amoxicillin.

Methods: We conducted a double-blind, randomized, placebo-controlled noninferiority trial involving children at primary health care centers in low-income communities in Karachi, Pakistan. Children who were 2 to 59 months of age and who met WHO criteria for nonsevere pneumonia with tachypnea were randomly assigned to a 3-day course of a suspension of amoxicillin (the active control) of 50 mg per milliliter or matched volume of placebo (the test regimen), according to WHO weight bands (500 mg every 12 hours for a weight of 4 to <10 kg, 1000 mg every 12 hours for a weight of 10 to <14 kg, or 1500 mg every 12 hours for a weight of 14 to <20 kg). The primary outcome was treatment failure during the 3-day course of amoxicillin or placebo. The prespecified noninferiority margin was 1.75 percentage points.

Results: From November 9, 2014, through November 30, 2017, a total of 4002 children underwent randomization (1999 in the placebo group and 2003 in the amoxicillin group). In the per-protocol analysis, the incidence of treatment failure was 4.9% among placebo recipients (95 of 1927 children) and 2.6% among amoxicillin recipients (51 of 1929 children) (between-group difference, 2.3 percentage points; 95% confidence interval [CI], 0.9 to 3.7). Results were similar in the intention-to-treat analysis. The presence of fever and wheeze predicted treatment failure. The number needed to treat to prevent one treatment failure was 44 (95% CI, 31 to 80). One patient (<0.1%) in each group died. Relapse occurred in 40 children (2.2%) in the placebo group and in 58 children (3.1%) in the amoxicillin group.

Conclusions: Among children younger than 5 years of age with nonsevere pneumonia, the frequency of treatment failure was higher in the placebo group than in the amoxicillin group, a difference that did not meet the noninferiority margin for placebo.

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Amoxicillin for 3 or 5 Days for Chest-Indrawing Pneumonia in Malawian Children

Amy-Sarah Ginsburg[1], Tisungane Mvalo[1], Evangelyn Nkwopara[1], Eric D McCollum[1], Melda Phiri[1], Robert Schmicker[1], Jun Hwang[1], Chifundo B Ndamala[1], Ajib Phiri[1], Norman Lufesi[1], Susanne May[1]

Abstract

Background: Evidence regarding the appropriate duration of treatment with antibiotic agents in children with pneumonia in low-resource settings in Africa is lacking.

Methods: We conducted a double-blind, randomized, controlled, noninferiority trial in Lilongwe, Malawi, to determine whether treatment with amoxicillin for 3 days is less effective than treatment for 5 days in children with chest-indrawing pneumonia (cough lasting <14 days or difficulty breathing, along with visible indrawing of the chest wall with or without fast breathing for age). Children not infected with human immunodeficiency virus (HIV) who were 2 to 59 months of age and had chest-indrawing pneumonia were randomly assigned to receive amoxicillin twice daily for either 3 days or 5 days. Children were followed for 14 days. The primary outcome was treatment failure by day 6; noninferiority of the 3-day regimen to the 5-day regimen would be shown if the percentage of children with treatment failure in the 3-day group was no more than 1.5 times that in the 5-day group. Prespecified secondary analyses included assessment of treatment failure or relapse by day 14.

Results: From March 29, 2016, to April 1, 2019, a total of 3000 children underwent randomization: 1497 children were assigned to the 3-day group, and 1503 to the 5-day group. Among children with day 6 data available, treatment failure had occurred in 5.9% in the 3-day group (85 of 1442 children) and in 5.2% (75 of 1456) in the 5-day group (adjusted difference, 0.7 percentage points; 95% confidence interval [CI], -0.9 to 2.4) - a result that satisfied the criterion for noninferiority of the 3-day regimen to the 5-day regimen. Among children with day 14 data available, 176 of 1411 children (12.5%) in the 3-day group and 154 of 1429 (10.8%) in the 5-day group had had treatment failure by day 6 or relapse by day 14 (between-group difference, 1.7 percentage points; 95% CI, -0.7 to 4.1). The percentage of children with serious adverse events was similar in the two groups (9.8% in the 3-day group and 8.8% in the 5-day group).

Conclusions: In HIV-uninfected Malawian children, treatment with amoxicillin for chest-indrawing pneumonia for 3 days was noninferior to treatment for 5 days

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Implementation of C-reactive protein point of care testing to improve antibiotic targeting in respiratory illness in Vietnamese primary care (ICAT): a study protocol for a cluster randomised controlled trial

Nga Thi Thuy Do[1], Rachel Claire Greer[2 3], Yoel Lubell[2 3], Sabine Dittrich[3 4], Maida Vandendorpe[4], Van Anh Nguyen[5], Pham Ngoc Thach[6], Ta Thi Dieu Ngan[6], Nguyen Van Kinh[6], Cao Hung Thai[7], Le Thi Kim Dung[7], Tu Nguyen Thi Cam[8], Thanh Ha Nguyen[8], Behzad Nadjm[8 3 9 10], H Rogier van Doorn[8 3], Sonia Lewycka[8 3 11]

Abstract

Introduction: C-reactive protein (CRP), a biomarker of infection, has been used widely in high-income settings to guide antibiotic treatment in patients presenting with respiratory illnesses in primary care. Recent trials in low- and middle-income countries showed that CRP testing could safely reduce antibiotic use in patients with non-severe acute respiratory infections (ARIs) and fever in primary care. The studies, however, were conducted in a research-oriented context, with research staff closely monitoring healthcare behaviour thus potentially influencing healthcare workers' prescribing practices. For policy-makers to consider wide-scale roll-out, a pragmatic implementation study of the impact of CRP point of care (POC) testing in routine care is needed.
Methods and analysis: A pragmatic, cluster-randomised controlled trial, with two study arms, consisting of 24 commune health centres (CHC) in the intervention arm (provision of CRP tests with additional healthcare worker guidance) and 24 facilities acting as controls (routine care). Comparison between the treatment arms will be through logistic regression, with the treatment assignment as a fixed effect, and the CHC as a random effect. With 48 clusters, an average of 10 consultations per facility per week will result in approximately 520 over 1 year, and 24 960 in total (12 480 per arm). We will be able to detect a reduction of 12% to 23% or more in immediate antibiotic prescription as a result of the CRP POC intervention. The primary endpoint is the proportion of patient consultations for ARI resulting in immediate antibiotic prescription. Secondary endpoints include the proportion of all patients receiving an antibiotic prescription regardless of ARI diagnosis, frequency of re-consultation, subsequent antibiotic use when antibiotics are not prescribed, referral and hospitalisation.
Ethics and dissemination: The study protocol was approved by the Oxford University Tropical Research Ethics Committee (OxTREC, Reference: 53-18), and the ethical committee of the National Hospital for Tropical Diseases in Vietnam (Reference:07/HDDD-NDTW/2019). Results from this study will be disseminated via meetings with stakeholders, conferences and publications in peer-reviewed journals. Authorship and reporting of this work will follow international guidelines.

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Efficacy of Adjunctive Zinc in Improving the Treatment Outcomes in Hospitalized Children with Pneumonia: A Randomized Controlled Trial

Lakkana Rerksuppaphol[1], Sanguansak Rerksuppaphol[2]

Abstract
Background: The mortality rate of pneumonia is high, placing a huge burden on developing countries. Healthcare professionals use zinc as an adjunctive treatment for children with pneumonia; however, this contradicts with some published reports. Thus, this study aimed to assess the efficacy of zinc supplementation on the treatment outcomes of pneumonia.
Methods: A randomized, double-blind, placebo-controlled trial was conducted on hospitalized children with pneumonia. The children randomly received either zinc bis-glycinate (15 mg elemental zinc) or placebo, twice per day. The primary outcome was the resolution time of pneumonia, and the secondary outcomes were the duration of hospitalization and the recovery times of each clinical symptom.

Results: Out of the 91 children, 65 (71.4%) were males. The resolution period of clinical pneumonia was significantly shorter in the zinc group than the placebo group (48 and 72 h, respectively; hazard ratio = 0.585, 95% confidence interval 0.377-0.908). Similarly, the hospitalization period and the resolution period of fever were shorter in the zinc group [96 and 144 h (p = 0.008), and 24 and 42 h (p = 0.002), respectively]. Children receiving zinc needed a median of 28 h to reach the normal level of oxygen saturation compared to 48 h required by children under placebo (p = 0.014).
Conclusion: Zinc supplementation enhanced the treatment outcomes of pneumonia, by reducing the resolution period of pneumonia and normalizing oxygen levels and body temperature. The length of hospital stay for children receiving zinc was shorter than those receiving placebo.

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Efficacy of zinc as adjunctive pneumonia treatment in children aged 2 to 60 months in low-income and middle-income countries: a systematic review and meta-analysis
Nick Brown[1], Antti Juhani Kukka[2], Andreas Mårtensson[3]
Abstract
Background: Despite advances in vaccination and case management, pneumonia remains the single largest contributor to early child mortality worldwide. Zinc has immune-enhancing properties, but its role in adjunctive treatment of pneumonia in low-income and middle-income countries (LMICs) is controversial and research still active.
Methods: Systematic review and meta-analysis of randomised controlled trials of zinc and placebo in pneumonia in children aged 2 to 60 months in LMICs. Databases included MEDLINE, the Cochrane Library, EMBASE, LILACS, SciELO, the WHO portal, Scopus, Google Scholar and ClinicalTrials.gov. Inclusion criteria included accepted signs of pneumonia and clear measure of outcome. Risk of bias was independently assessed by two authors. ORs with 95% CI were used for calculating the pooled estimate of dichotomous outcomes including treatment failure and mortality. Time to recovery was expressed as HRs. Sensitivity analyses considering risk of bias and subgroup analyses for pneumonia severity were performed.
Results: We identified 11 trials published between 2004 and 2019 fulfilling the a priori defined criteria, 7 from South Asia and 3 from Africa and 1 from South America. Proportional treatment failure was comparable in both zinc and placebo groups when analysed for all patients (OR 0.95 (95% CI 0.80 to 1.14)) and only for those with severe pneumonia (OR 0.93 (95% CI 0.75 to 1.14)). No difference was seen in mortality between zinc and placebo groups (OR 0.64 (95% CI 0.31 to 1.31)). Time to recovery from severe pneumonia did not differ between the treatment and control groups for patients with severe pneumonia (HR 1.01 (95% CI 0.89 to 1.14)). Removal of four studies with high risk of bias made no difference to the conclusions.
Conclusion: There is no evidence that adjunctive zinc treatment improves recovery from pneumonia in children in LMICs.

Bronchiolitis

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Nebulized Magnesium Sulphate in Bronchiolitis: A Randomized Controlled Trial

Roma Debbarma[1], Daisy Khera[2], Surjit Singh[3], Nisha Toteja[4], Bharat Choudhary[5], Kuldeep Singh[1]

Abstract

Objective: To evaluate the efficacy and safety of nebulized magnesium sulphate as a bronchodilator in young children aged 1-24 mo with moderate to severe bronchiolitis in comparison to standard therapy.

Methods: This was an open labeled randomized controlled trial comprising 60 children with moderate to severe bronchiolitis which was randomly assigned to 2 groups. Intervention group received nebulization with 3 mL of 3.2% magnesium sulphate ($MgSO_4$) (iso-osmolar) every 4 hourly for 24 h in addition to standard care and the control group received standard care alone. The primary outcome measure was to compare the improvement of bronchiolitis severity score (BSS) and length of hospitalization. The secondary outcome was to measure the need for noninvasive ventilation, need for admission to intensive care unit (ICU) in the initial visit, to evaluate the safety of magnesium sulphate and need for clinic revisit, hospital readmission and ICU readmission within 2 wk after discharge in both the groups.

Results: The mean age of children allocated in the control group was 7.4 ± 5.1 mo and 7.7 ± 4.5 mo in the intervention group. There was no significant difference with respect to improvement of BSS or reduced length of hospitalization in both the groups ($p > 0.05$). BSS monitored sequentially after enrollment at 1, 2, 4, 8, 12, 16, and 24 h did not show statistically significant differences between the groups. Mean length of hospital stay was 2.89 ± 2.25 d in treatment group and 2.96 ± 1.86 d in control group ($p = 0.902$). No adverse events were observed in both the groups.

Conclusion: Nebulized magnesium sulphate is not superior to standard therapy in children with moderate to severe bronchiolitis.

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Magnesium sulphate for treating acute bronchiolitis in children up to two years of age

Sudha Chandelia[1], Dinesh Kumar[2], Neelima Chadha[3], Nishant Jaiswal[4]

Abstract

Background: Acute bronchiolitis is a significant burden on children, their families and healthcare facilities. It mostly affects children younger than two years of age. Treatment involves adequate hydration, humidified oxygen supplementation, and nebulisation of medications, such as salbutamol, epinephrine, and hypertonic saline. The effectiveness of magnesium sulphate for acute bronchiolitis is unclear.

Objectives: To assess the effects of magnesium sulphate in acute bronchiolitis in children up to two years of age.

Search methods: We searched CENTRAL, MEDLINE, Embase, LILACS, CINAHL, and two trials registries to 30 April 2020. We contacted trial authors to identify additional studies. We

searched conference proceedings and reference lists of retrieved articles. Unpublished and published studies were eligible for inclusion.
Selection criteria: Randomised controlled trials (RCTs) and quasi-RCTs, comparing magnesium sulphate, alone or with another treatment, with placebo or another treatment, in children up to two years old with acute bronchiolitis. Primary outcomes were time to recovery, mortality, and adverse events. Secondary outcomes were duration of hospital stay, clinical severity score at 0 to 24 hours and 25 to 48 hours after treatment, pulmonary function test, hospital readmission within 30 days, duration of mechanical ventilation, and duration of intensive care unit stay.
Data collection and analysis: We used standard methodological procedures expected by Cochrane. We used GRADE methods to assess the certainty of the evidence.
Main results: We included four RCTs (564 children). One study received funding from a hospital and one from a university; two studies did not report funding sources. Comparator interventions differed among all four trials. Studies were conducted in Qatar, Turkey, Iran, and India. We assessed two studies to be at an overall low risk of bias, and two to be at unclear risk of bias, overall. The certainty of the evidence for all outcomes and comparisons was very low except for one: hospital re-admission rate within 30 days of discharge for magnesium sulphate versus placebo. None of the studies measured time to recovery, duration of mechanical ventilation, duration of intensive care unit stay, or pulmonary function. There were no events of mortality or adverse effects for magnesium sulphate compared with placebo (1 RCT, 160 children). The effects of magnesium sulphate on clinical severity are uncertain (at 0 to 24 hours: mean difference (MD) on the Wang score 0.13, 95% confidence interval (CI) -0.28 to 0.54; and at 25 to 48 hours: MD on the Wang score -0.42, 95% CI -0.84 to -0.00). Magnesium sulphate may increase hospital re-admission rate within 30 days of discharge (risk ratio (RR) 3.16, 95% CI 1.20 to 8.27; 158 children; low-certainty evidence). None of our primary outcomes were measured for magnesium sulphate compared with hypertonic saline (1 RCT, 220 children). Effects were uncertain on the duration of hospital stay in days (MD 0.00, 95% CI -0.28 to 0.28), and on clinical severity on the Respiratory Distress Assessment Instrument (RDAI) score at 25 to 48 hours (MD 0.10, 95% CI -0.39 to 0.59). There were no events of mortality or adverse effects for magnesium sulphate, with or without salbutamol, compared with salbutamol (1 RCT, 57 children). Effects on the duration of hospital stay were uncertain (magnesium sulphate: 24 hours (95% CI 25.8 to 47.4), magnesium sulphate + salbutamol: 20 hours (95% CI 15.3 to 39.0), and salbutamol: 24 hours (95% CI 23.4 to 76.9)). None of our primary outcomes were measured for magnesium sulphate + epinephrine compared with no treatment or normal saline + epinephrine (1 RCT,120 children). Effects were uncertain for the duration of hospital stay in hours (MD -0.40, 95% CI -3.94 to 3.14), and for RDAI scores (0 to 24 hours: MD -0.20, 95% CI -1.06 to 0.66; and 25 to 48 hours: MD -0.90, 95% CI -1.75 to -0.05).
Authors' conclusions: There is insufficient evidence to establish the efficacy and safety of magnesium sulphate for treating children up to two years of age with acute bronchiolitis. No evidence was available for time to recovery, duration of mechanical ventilation and intensive care unit stay, or pulmonary function. There was no information about adverse events for some comparisons. Well-designed RCTs to assess the effects of magnesium sulphate for children with acute bronchiolitis are needed. Important outcomes, such as time to recovery and adverse events should be measured.

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Antibiotic therapy versus no antibiotic therapy for children aged 2 to 59 months with WHO-defined non-severe pneumonia and wheeze

Zohra S Lassi[1], Zahra Ali Padhani[2], Jai K Das[3], Rehana A Salam[3], Zulfiqar A Bhutta[4]

Abstract

Background: Worldwide, pneumonia is the leading cause of death amongst children under five years of age, and accounts for approximately two million deaths annually. Pneumonia can be classified according to the World Health Organization (WHO) guidelines. Classification includes assessment of certain clinical signs and symptoms, and the severity of the disease. Treatment is then tailored according to the classification. For non-severe pneumonia, the WHO recommends treatment with oral antibiotics. We used the 2014 WHO definition of non-severe pneumonia for this review: an acute episode of cough, or difficulty in breathing, combined with fast breathing and chest indrawing. The WHO recommends treating non-severe pneumonia with oral antibiotics. Pneumonia is more commonly caused by viruses that do not require antibiotic treatment, but pneumonia caused by bacteria needs management with antibiotics to avoid complications. There is no clear way to quickly distinguish between viral and bacterial pneumonia. It is considered safe to give antibiotics, however, this may lead to the development of antibiotic resistance, and thus, limit their use in future infections. Therefore, it is essential to explore the efficacy of antibiotics for children with WHO-defined non-severe pneumonia and wheeze.

Objectives: To evaluate the efficacy of antibiotic therapy versus no antibiotic therapy for children aged 2 to 59 months with WHO-defined non-severe pneumonia and wheeze.

Search methods: We searched CENTRAL, MEDLINE, Embase, four other databases, and two trial registers (December 2020).

Selection criteria: We included randomised controlled trials (RCTs) evaluating the efficacy of antibiotic therapy versus no antibiotic therapy for children, aged 2 to 59 months, with non-severe pneumonia and wheeze. We defined non-severe pneumonia as 'a cough or difficulty in breathing, with rapid breathing (a respiratory rate of 50 breaths per minute or more for children aged 2 to 12 months, or a respiratory rate of 40 breaths per minute or more for children aged 12 to 59 months), chest indrawing and wheeze'. We excluded trials involving children with severe or very severe pneumonia, and non-RCTs.

Data collection and analysis: Our primary outcomes were clinical cure and treatment failure; secondary outcomes were relapse, mortality, and treatment harms. We used standard methodological procedures expected by Cochrane. We used GRADE to assess the certainty of the evidence. Two review authors independently assessed the search results, extracted data, assessed risk of bias and the certainty of the evidence. We contacted the authors of two included trials and the author of the trial awaiting classification to obtain missing numerical outcome data.

Main results: We included three trials involving 3256 children aged between 2 to 59 months, who exhibited features of non-severe pneumonia with wheeze. The included trials were multi-centre, double-blind, randomised, placebo-controlled trials carried out in Malawi, Pakistan, and India. The children were treated with a three-day course of amoxicillin or placebo, and were followed up for a total of two weeks. We assessed the included trials at overall low risk of bias for random sequence generation, allocation concealment, blinding, attrition bias, and selective reporting. Only one trial was assessed to be at high risk for

blinding of outcome assessors. One trial is awaiting classification Antibiotic therapy may result in a reduction of treatment failure by 20% (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.68 to 0.94; three trials; 3222 participants; low-certainty evidence). Antibiotic therapy probably results in little or no difference to clinical cure (RR 1.02, 95% CI 0.96 to 1.08; one trial; 456 participants; moderate-certainty evidence), and in little or no difference to relapse (RR 1.00, 95% CI 0.74 to 1.34; three trials; 2795 participants; low-certainty evidence), and treatment harms (RR 0.81, 95% CI 0.60 to 1.09; three trials, 3253 participants; low-certainty evidence). Two trials (2112 participants) reported on mortality; no deaths occurred in either group. One trial reported cases of hospitalisation, diarrhoea (with and without dehydration), rash (without itch), tremors, mild nausea and vomiting.
Authors' conclusions: We do not currently have enough evidence to support or challenge the continued use of antibiotics for the treatment of non-severe pneumonia. There is a clear need for RCTs to address this question in children aged 2 to 59 months with 2014 WHO-defined non-severe pneumonia and wheeze.

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Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis

Steven M Brunwasser[1], Brittney M Snyder[2], Amanda J Driscoll[3], Deshayne B Fell[4], David A Savitz[5], Daniel R Feikin[6], Becky Skidmore[7], Niranjan Bhat[8], Louis J Bont[9], William D Dupont[2], Pingsheng Wu[2], Tebeb Gebretsadik[2], Patrick G Holt[10], Heather J Zar[11], Justin R Ortiz[3], Tina V Hartert[12]

Abstract
Background: Although a positive association has been established, it is unclear whether lower respiratory tract infections (LRTIs) with respiratory syncytial virus (RSV) cause chronic wheezing illnesses. If RSV-LRTI were causal, we would expect RSV-LRTI prevention to reduce the incidence of chronic wheezing illnesses in addition to reducing acute disease. We aimed to evaluate the strength of evidence for a causal effect of RSV-LRTI on subsequent chronic wheezing illness to inform public health expectations for RSV vaccines.
Methods: We did a systematic review and meta-analysis of observational studies evaluating the association between RSV-LRTI and subsequent wheezing illness (exposure studies) and studies evaluating the association between RSV immunoprophylaxis and subsequent wheezing illness (immunoprophylaxis studies). Exposure studies were included if the exposure group members had an LRTI with laboratory-confirmed RSV and if the exposure ascertainment period began before 2 years of age and ended before 5 years of age. We required a wash-out period of more than 30 days between the index RSV-LRTI and the outcome measurement to allow for resolution of the acute illness. Comparisons between RSV-LRTI and non-RSV-LRTI were not included. Immunoprophylaxis studies were included if they measured the association with subsequent wheezing illness relative to a control group, either in a randomised controlled trial (RCT) or an observational design. For the immunoprophylaxis drugs in question, we required evidence of efficacy in targeting RSV-LRTI from at least one RCT to ensure biological plausibility. All variations of wheezing illness were combined into a single outcome that refers broadly to asthma or any other respiratory illness

with wheezing symptoms. Ovid MEDLINE and Embase databases were searched from inception up to Aug 28, 2018. We evaluated whether data from exposure studies could provide evidence against the most viable non-causal theory that RSV-LRTI is a marker of respiratory illness susceptibility rather than a causal factor. Additionally, we tested whether RSV immunoprophylaxis reduces the odds of subsequent wheezing illnesses. We used a random-effects modelling framework and, to accommodate studies providing multiple correlated estimates, robust variance estimation meta-regressions. Meta-regression coefficients (b) quantify differences between exposure and comparator groups on the $\log_e$ odds ratio ($\log_e$ OR) scale.
Findings: From 14 235 records we identified 57 eligible articles that described 42 studies and provided 153 effect estimates. 35 studies estimated the direct effect of RSV-LRTI on wheezing illnesses (exposure studies) and eight evaluated the effect of RSV immunoprophylaxis (immunoprophylaxis studies). Exposure studies that adjusted for genetic influences yielded a smaller mean adjusted OR estimate (aOR_+ 2·45, 95% CI 1·23-4·88) compared with those that did not (4·17, 2·36-7·37), a significant difference (b 0·53, 95% CI 0·04-1·02). Infants who were not protected with RSV immunoprophylaxis tended to have higher odds of subsequent wheezing illness, as we would expect if RSV-LRTI were causal, but the effect was not significant (OR_+ 1·21, 95% CI 0·73-1·99). There was generally a high threat of confounding bias in the observational studies. Additionally, in both the observational studies and immunoprophylaxis RCTs, there was high risk of bias due to missing outcome data.
Interpretation: Our findings, limited to exposure and immunoprophylaxis studies, do not support basing policy decisions on an assumption that prevention of RSV-LRTI will reduce recurrent chronic wheezing illnesses.

Oxygen therapy and CPAP

Adolescent health

Adolescent nutrition

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Impact of daily-supervised administration of a package of iron and folic acid and vitamin B_{12} on hemoglobin levels among adolescent girls (12-19 years): a cluster randomized control trial

Aakriti Gupta[1], Shashi Kant[2], Lakshmy Ramakrishnan[3], Ravindra Mohan Pandey[4], Ritika Khandelwal[1], Umesh Kapil[5], Harshpal Singh Sachdev[6]

Abstract
Objective: The prevalence of anemia has remained high among Indian adolescent girls over the past decade, despite the ongoing iron and folic acid (IFA) supplementation program. This

study was conducted to assess the impact of daily supplementation of a package of IFA with vitamin B_{12} on hemoglobin levels among adolescent girls.
Methods: A community-based cluster-randomized trial was conducted in the rural block of Faridabad District, Haryana, India in the year 2017. A total of 760 adolescent girls in the age group of 12-19 years with mild and moderate anemia were selected from government schools. Daily-supervised administration of iron and folic acid was conducted for 90 days: experimental group-IFA (iron (60 mg), folic acid (500) mcg), and cyanocobalamin (1000 mcg), control group-IFA and placebo. Hemoglobin, serum ferritin, and vitamin B_{12} levels were assessed at baseline and endline.
Results: Two-hundred adolescent girls completed 90 doses of daily supplementation. The mean hemoglobin (experimental group: 1.3 ± 1.0 g/dL, control group: 1.6 ± 1.2 g/dL, P = 0.004) and ferritin levels (experimental group: 18.6 ± 31.5 ng/mL, control group: 18.8 ± 35.0 ng/mL, P = 0.188) increased in both the control and experiment groups. Serum vitamin B_{12} deficiency significantly reduced to 2.5% in the experimental group and ferritin deficiency alleviated in more than 96% of the girls post intervention.
Conclusions: Daily supplementation of IFA with/without vitamin B_{12} for 90 days eliminated iron, vitamin B_{12} deficiency and reduced the overall proportion of anemia by 53.5%. However, addition of vitamin B_{12} to IFA supplementation had no impact on improving the hemoglobin levels among adolescent girls. The present study does not recommend provision of vitamin B_{12} for prevention and treatment of anemia in this population group.

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Impact of a behaviourally focused nutrition education intervention on attitudes and practices related to eating habits and activity levels in Indian adolescents

Panchali Moitra[1], Jagmeet Madan[1], Preeti Verma[2]

Abstract
Objective: To evaluate the effectiveness of a behaviourally focused nutrition education (NE) intervention based on the Health Belief Model (HBM) to improve knowledge, attitudes and practices (KAP) related to eating habits and activity levels in 10-12-year-old adolescents in Mumbai, India.
Design: School-based cluster randomised controlled trial. The experimental group (EG) received weekly NE and three parent sessions over 12 weeks; no sessions were conducted for the control group (CG). The theoretical framework of HBM and focus group discussion results guided the development of behaviour change communication strategies and NE aids. KAP were measured using a validated survey instrument, administered at baseline and endline in EG and CG. Paired and independent t tests determined within-group and between-group changes in pre-post scores.
Setting: Two aided and two private schools that were randomly allocated to either an EG or CG.
Participants: Adolescent boys and girls (n 498; EG n 292 and CG n 206).
Results: EG reported improvements in mean knowledge (39·3%), attitude (7·3 %), diet (9·6 %) and activity practice (9·4%) scores from pre to post intervention. No significant changes were observed in CG. Significant improvements in scores associated with perceived benefits, barriers and self-efficacy, breakfast and vegetable consumption, and moderate-to-vigorous activities were observed in EG.

Conclusions: Integrating NE into the academic curriculum and adopting evidence-based lessons that entail targeted information delivery and participatory activities can improve knowledge, foster right attitudes and facilitate better eating and activity-related practices in Indian adolescents.

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Systematic Review: Effect of Health Education Intervention on Improving Knowledge, Attitudes and Practices of Adolescents on Malnutrition

Ruth Charles Shapu[1,2], Suriani Ismail[1], Norliza Ahmad[1], Poh Ying Lim[1], Ibrahim Abubakar Njodi[3]

Abstract

Adolescence is a phase in the life cycle of human beings. Adequate knowledge, attitudes and practices towards malnutrition are necessary for proper growth and development and for their future children. This systematic review aimed to determine the effect of health education intervention to improve the knowledge, attitudes and practices of adolescents on malnutrition. PubMed, Scopus, clinical trials, CINAHL, SAGE, Science Direct and Medline were searched according to Preferred Reporting Item for Systematic Reviews and Meat-analysis (PRISMA) guidelines to identified published studies from January 2013 to December 2019 based on the inclusion and exclusion criteria. A total of eight studies were included in this review. Data extraction was done based on randomized controlled trial only. Three out of the eight studies had low risk of bias, the overall evidence of the study was moderate. Findings from this study suggest that health education intervention among adolescents have significantly improved their knowledge, attitudes and practices. More specific interventions should be conducted in low and middle income countries since they bear more of the burden of malnutrition globally.

Adolescent sexual and reproductive health

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Parent-child communication about sexual issues in Zambia: a cross sectional study of adolescent girls and their parents

Katja Jezkova Isaksen[1,2], Patrick Musonda[3], Ingvild Fossgard Sandøy[4]

Abstract

Background: Parent-child communication about sexual issues can reduce risky sexual behaviour amongst adolescents. Risky sexual behaviour is of concern in sub-Saharan Africa where the prevalence of early pregnancy, unsafe abortion and HIV are high. Parent-child communication about sexual issues presents a feasible approach for reducing sexual risk amongst adolescents in sub-Saharan Africa but limited research exists from the region. This

study from Zambia examines the sociodemographic and psychosocial factors that are associated with whether parents communicate with their daughters about sexual issues.
Methods: Data from a cluster randomized controlled trial examining the effect of interventions aiming to reduce teenage pregnancy and school drop out in Zambia was used. The data was collected between January-July in 2018 and consists of structured, face to face interviews with 4343 adolescent girls and 3878 parents. Cross sectional analyses examined the associations between parent-child communication about sexual issues and sociodemographic and psychosocial characteristics using univariate and multivariable logistic regression models.
Results: Adolescent girls who felt connected to their parents and those who perceived their parents to be comfortable in communicating about sex, were more likely to speak to their parents about sexual issues than those who did not (AOR 1.23, 95% CI 1.01-1.52; and AOR 2.94, 95% CI 2.45-3.54, respectively). Girls whose parents used fear-based communication about sexual issues, and those who perceived their parents as being opposed to education about contraception, were less likely to communicate with their parents about sex than those who did not (AOR 0.76, 95% CI 0.65-0.89; and AOR 0.76, 95% CI 0.63-0.91, respectively). Girls enrolled in school were less likely to communicate with their parents about sex than those out of school (AOR 0.56, 95% CI 0.44-0.71).
Conclusion: Parenting style, children's perception of parental attitudes and parental communication styles are associated with whether parents and children communicate about sexual issues. This may imply that parents can improve the chances of communicating with their children about sex by conveying non-judgemental attitudes, using open communication styles with neutral messages and appearing comfortable whilst displaying positive attitudes towards communication around sex and contraceptive use.

Lancet Child Adolesc Health. 2021 Feb;5(2):122-132.
doi: 10.1016/S2352-4642(20)30335-7. Epub 2021 Jan 6.

Uptake of and factors associated with testing for sexually transmitted infections in community-based settings among youth in Zimbabwe: a mixed-methods study

Kevin Martin[1], Ioana D Olaru[2], Nyasha Buwu[3], Tsitsi Bandason[3], Michael Marks[4], Ethel Dauya[3], Joice Muzangwa[3], David Mabey[4], Chido Dziva Chikwari[2], Suzanna C Francis[5], Mandikudza Tembo[6], Constancia Mavodza[7], Victoria Simms[8], Constance R S Mackworth-Young[4], Anna Machiha[9], Katharina Kranzer[10], Rashida A Ferrand[2]

Abstract
Background: The prevalence of sexually transmitted infections (STIs) among youth is high in sub-Saharan Africa. We investigated the uptake of testing for and prevalence of Chlamydia trachomatis (chlamydia) and Neisseria gonorrhoeae (gonorrhoea) infections among youth in community-based settings in Zimbabwe, and explored the facilitators and barriers to testing.
Methods: This study was nested within a cluster randomised trial of community-based delivery of integrated HIV and sexual and reproductive health services for youth aged 16-24 years. Chlamydia and gonorrhoea testing via urine samples using the Xpert CT/NG test was offered in the four intervention clusters in Harare, Zimbabwe. Factors associated with testing uptake were investigated in a subset of participants (n=257) using hierarchical multivariate logistic regression. In-depth interviews with a separate purposively selected sample (n=26)

explored facilitators and barriers to STI testing and partner notification and were analysed using thematic analysis.
Findings: Between June 1, 2019, and Jan 31, 2020, there were 6200 attendances by 4440 participants (78·2% women, 21·8% men) median age 20·3 (IQR 17·9-22·8) years. 1478 participants had 1501 tests done, and 248 tests were positive and 1253 tests were negative for chlamydia or gonorrhoea, or both. STI test uptake was 33·3% (95% CI 31·9-34·7), increasing from 11·7% in June, 2019, to 37·1% in January, 2020. The prevalence of chlamydia or gonorrhoea, or both, was 16·5% (95% CI 14·7-18·5; 248 of 1501), with only seven participants (3%) showing symptoms. The overall yield of testing was 4·0% (95% CI 3·5-4·5; 248 of 6200). Uptake was associated with having symptoms (adjusted odds ratio [OR] 14·8, 95% CI 1·66-132·07) and negatively associated with being single (adjusted OR 0·33, 95% CI 0·13-0·84) or having a boyfriend or girlfriend (adjusted OR 0·19, 95% CI 0·087-0·43) compared with being married, and being a student compared with being employed (adjusted OR 0·26, 95% CI 0·10-0·68). Perceived risk and symptoms of STIs were motivators for testing whereas misinformation, anticipated stigma, and concern about confidentiality were barriers.
Interpretation: The prevalence of chlamydia or gonorrhoea, or both, was high among youth but only a minority were symptomatic. Therefore most infections would remain untreated without access to STI testing. Provision of education, counselling, and confidentiality are essential to improve uptake and acceptability of STI testing.

Nat Commun. 2020 Nov 4;11(1):5578.
doi: 10.1038/s41467-020-19382-9.

Hormonal contraception alters vaginal microbiota and cytokines in South African adolescents in a randomized trial

Christina Balle[1], Iyaloo N Konstantinus[1], Shameem Z Jaumdally[1], Enock Havyarimana[1], Katie Lennard[2], Rachel Esra[1], Shaun L Barnabas[1 3], Anna-Ursula Happel[1], Zoe Moodie[4], Katherine Gill[3], Tanya Pidwell[3], Ulas Karaoz[5], Eoin Brodie[5 6], Venessa Maseko[7], Hoyam Gamieldien[1], Steven E Bosinger[8], Landon Myer[9], Linda-Gail Bekker[3], Jo-Ann S Passmore[1 10], Heather B Jaspan[11 12 13]

Abstract

Young women in sub-Saharan Africa are disproportionally affected by HIV infection and unintended pregnancies. However, hormonal contraceptive (HC) use may influence HIV risk through changes in genital tract microbiota and inflammatory cytokines. To investigate this, 130 HIV negative adolescent females aged 15-19 years were enrolled into a substudy of UChoose, an open-label randomized crossover study (NCT02404038), comparing acceptability and contraceptive product preference as a proxy for HIV prevention delivery methods. Participants were randomized to injectable norethisterone enanthate (Net-En), combined oral contraceptives (COC) or etonorgesterol/ethinyl estradiol combined contraceptive vaginal ring (CCVR) for 16 weeks, then crossed over to another HC for 16 weeks. Cervicovaginal samples were collected at baseline, crossover and exit for characterization of the microbiota and measurement of cytokine levels; primary endpoints were cervical T cell activation, vaginal microbial diversity and cytokine concentrations. Adolescents randomized to COCs had lower vaginal microbial diversity and relative abundance of HIV risk-associated taxa compared to Net-En or CCVR. Cervicovaginal inflammatory cytokine concentrations were significantly higher in adolescents randomized

to CCVR compared to COC and Net-En. This suggests that COC use may induce an optimal vaginal ecosystem by decreasing bacterial diversity and inflammatory taxa, while CCVR use is associated with genital inflammation.

Sex Transm Infect. 2021 Mar;97(2):112-117.
doi: 10.1136/sextrans-2020-054483. Epub 2020 Sep 28.

Hormonal contraception and risk of STIs and bacterial vaginosis in South African adolescents: secondary analysis of a randomised trial

Christina Balle[1], Katherine Gill[2], Iyaloo N Konstantinus[1], Shameem Z Jaumdally[1], Katie Lennard[3], Rachel Esra[1], Anna-Ursula Happel[1], Shaun L Barnabas[1 4], Hoyam Gamieldien[1], Tanya Pidwell[2], Venessa Maseko[5], Maia Lesosky[6], Landon Myer[6], Jo-Ann S Passmore[1 7], Linda-Gail Bekker[# 2], Heather B Jaspan[# 8 9 10]

Abstract

Objectives: Young women in sub-Saharan Africa are at high risk of STIs and unintended pregnancies, yet hormonal contraceptive (HC) use may affect STI risk. We compared the influence of three HCs on the incidence and prevalence of STIs and bacterial vaginosis (BV) in South African adolescents.

Methods: One hundred and thirty adolescents between 15 and 19 years were randomised to the injectable norethisterone enanthate (Net-En), combined oral contraceptives (COC) (Triphasil or Nordette) or a combined contraceptive vaginal ring (CCVR; NuvaRing) for 16 weeks (clinicaltrials.gov/NCT02404038). Vaginal samples were collected at baseline and 16 weeks post contraceptive initiation for STI and BV testing.

Results: In an intention-to-treat analysis, no significant differences in BV prevalence were found between study arms. The overall incidence of any STI at follow-up was high: 16.2% in the COC arm; 25.7% in the Net-En arm; and 37.1% in the CCVR arm. The incidence rate (IR) of any STI was similar between Net-En (IR 0.74 (95% CI 0.34 to 1.41)) and the oestrogen-containing contraceptives (IR 0.78 (95% CI 0.47 to 1.22)). A lower IR of *Chlamydia trachomatis* (incidence rate ratio (IRR) 0.68 (95% CI 0.19 to 1.99)) and *Neisseria gonorrhoeae* (IRR 0.25 (95% CI 0.01 to 1.35)) but a higher IR of *Mycoplasma genitalium* (IRR 16.0 (95% CI 2.96 to 400)), was observed in the Net-En arm compared with the oestrogen-containing contraceptives, although the overall incidence of *M. genitalium* was low (4.7%). In an exploratory analysis, the risk of any STI and *N. gonorrhoeae* was lower in the COC arm compared with CCVR. A per-protocol analysis yielded similar results.

Conclusion: Our results suggest that use of Net-En may be associated with increased risk of *M. genitalium* compared with oestrogen-containing contraceptives but not with overall STI risk. COC use may decrease STI risk relative to CCVR.

Prev Sci. 2020 Nov;21(8):1065-1080.
doi: 10.1007/s11121-020-01143-1.

Changes in Family-Level Attitudes and Norms and Association with Secondary School Completion and Child Marriage Among Adolescent Girls: Results from an Exploratory Study Nested Within a Cluster-Randomised Controlled Trial in India

Ravi Prakash[1 2], Tara S Beattie[3], Beniamino Cislaghi[3], Parinita Bhattacharjee[4], Prakash Javalkar[5], Satyanarayana Ramanaik[5], Raghavendra Thalinja[5], Calum Davey[3], Mitzy Gafos[3], Charlotte Watts[3], Martine Collumbien[3], Stephen Moses[4], Shajy Isac[4 6], Lori Heise[3 7]

Abstract

We evaluated the impact of Samata, a 3-year multilayered intervention among scheduled caste/scheduled tribe (SC/ST) adolescent girls in rural northern Karnataka, on family-level (parents or guardian) attitudes and direct and indirect norms related to child marriage and girl's education. Endline data from 1840 family members were used to assess the effect of Samata on attitudes and norms related to schooling and child marriage, while data from 4097 family members (including 2257 family members at baseline) were used to understand the shifts in attitudes and norms over the period 2014-2017. Overall, we found that the programme had little impact on family-level attitudes and norms. However, there were shifts in some attitudes, norms and perceived sanctions between baseline (when girls were aged 13-14 years) and endline (when girls were aged 15-16 years), with some becoming more progressive (e.g. direct norms related to child marriage) and others more restrictive (e.g. norms around girls completing secondary education and norms related to child marriage and educational drop-out, blaming girls for eve teasing and limiting girls' mobility so as to protect family honour). Moreover, non-progressive norms related to marriage and education were strongly associated with child marriage and secondary school non-completion among adolescent girls in this rural setting. Norms hypothesised to be important for marriage and schooling outcomes were indeed associated with these outcomes, but the intervention was not able to significantly shift these norms. In part, this may have been due to the intervention focusing much of its initial efforts on working with girls alone rather than family members, the relevant reference group. Future interventions that seek to affect norms should conduct formative research to clarify the specific norms affecting the outcome(s) of interest; likewise, programme planners should ensure that all activities engage those most influential in enforcing the norm(s) from the beginning.

Contracept Reprod Med. 2020 Oct 31;5(1):31.
doi: 10.1186/s40834-020-00134-5.

Effectiveness of a mobile phone application to increase access to sexual and reproductive health information, goods, and services among university students in Uganda: a randomized controlled trial

Elly Nuwamanya[1 2], Robinah Nalwanga[3], Afra Nuwasiima[3], Janet U Babigumira[3], Francis T Asiimwe[3], Joseph B Babigumira[4], Vitalis P Ngambouk[5]

Abstract

Background: University students are one of the most vulnerable groups to sexual reproductive health [SRH] threats like sexually transmitted infections [STIs], unwanted pregnancies, and unsafe abortions and often have limited access to SRH information, goods, and services. This study assessed the effectiveness of using a mobile phone application (APP) to increase access to SRH information, goods, and services among university students in Uganda.

Methods: Using data from a double-blinded randomized controlled trial, participants were randomly assigned to both the intervention (APP) and control (standard of care) arms. We executed descriptive analyses for baseline demographic characteristics by intervention,

difference in difference (DID), and quantile regression analyses for both primary and secondary outcomes.
Results: The median age of participants was 21 years of age, and the majority were female (over 60%), unemployed (over 85%) and Christian (90%). Over 50% were resident in off-campus hostels and in a relationship. Between baseline and end-line, there was a significant increase in SRH knowledge score (DID = 2, P < 0.001), contraceptive use (DID = 6.6%, P < 0.001), HIV Voluntary testing and counselling (DID = 17.2%, P < 0.001), STI diagnosis and treatment (DID = 12.9%, P < 0.001), and condom use at last sex (DID = 4%,P = 0.02) among students who used the APP. There was a significant 0.98 unit increase in knowledge score (adjusted coefficient = 0.98, P < 0.001), a significant 1.6-fold increase in odds of contraceptive use (adjusted coefficient = 1.6, P = 0.04), a significant 3.5-fold increase in HIV VCT (adjusted coefficient = 3.5, P < 0.001), and a significant 2-fold increase in odds of STI testing and treatment (adjusted coefficient = 1.9, P < 0.001) after adjusting for demographic characteristics among APP users compared to the control group.
Conclusion: A mobile phone application increased sexual and reproductive health information (knowledge score), access to goods (contraceptives), and services (HIV voluntary testing and counseling and sexually transmitted infection diagnosis and management) among sexually active university students in Uganda. Further technical development, including the refinement of youth-friendly attributes, extending access to the app with other platforms besides android which was pilot tested, as well as further research into potential economic impact and paths to sustainability, is needed before the app is deployed to the general youth population in Uganda and other low-income settings.

AIDS Behav. 2021 Mar 27.
doi: 10.1007/s10461-021-03242-8. Online ahead of print.
A Systematic Review of Randomized Controlled Trials of School Based Interventions on Sexual Risk Behaviors and Sexually Transmitted Infections Among Young Adolescents in Sub-Saharan Africa
Nosipho Shangase[#1,2], Ayesha B M Kharsany[#3,4], Nonzwakazi P Ntombela[2], Audrey Pettifor[2], Lyle R McKinnon[2,5]
Abstract
Young adolescents in Sub-Saharan Africa (SSA) are at high risk of involvement in sexual risk behaviors; and curable sexually transmitted infections (STI), herpes simplex virus type 2 (HSV-2), human immunodeficiency virus (HIV) and unintended pregnancies remain persistently high in this population. Evidence based strategies are urgently needed to improve these outcomes. The aim of this systematic review was to synthesize the evidence from randomized controlled trials (RCT) to determine whether school-based interventions promote safe sex behaviors, reduce sexual risk behaviors and risk of curable STIs, HSV-2, HIV and unintended pregnancies among young adolescents aged 9-19 years in SSA. Electronic databases were searched for published studies and manual searches were conducted through reviewing of references of cited literature in the English language up to December 2019. Two independent reviewers screened and abstracted the data. We identified 428 articles and data from nine RCTs (N = 14,426 secondary school students) that fulfilled the selection criteria were analysed. Two studies measured pregnancy as an outcome and showed significant declines in unintended pregnancies. Of the five studies that measured

HIV/AIDS related-knowledge, condom-use outcomes (normative beliefs, knowledge, and self-efficacy) and attitudes to HIV testing, four showed significant improvements. Of the six studies that measured sexual debut, four reported moderate but non-significant declines and in two studies sexual debut information was either incomplete or unreliable. One study measured curable STIs and found no significant declines; whilst the second study that measured HSV-2 and HIV, no significant declines were observed. This review highlights the need to undertake well-designed research studies to provide evidence on the impact of interventions on curable STIs, HSV-2 and HIV, critical to improving the health of young adolescents.

Adolescent mental health

BMC Public Health. 2020 Nov 25;20(1):1792.
doi: 10.1186/s12889-020-09937-2.

Prevalence and correlates of depressive symptoms among high school adolescent girls in southern Uganda

Proscovia Nabunya[1], Christopher Damulira[2], William Byansi[2], Joelynn Muwanga[2], Ozge Sensoy Bahar[2], Flavia Namuwonge[2], Eloho Ighofose[2], Rachel Brathwaite[2], Wilberforce Tumwesige[2], Fred M Ssewamala[2]

Abstract

Background: In sub-Saharan Africa (SSA), adolescent girls and young women are three times more likely than boys to have depressive disorders. Understanding adolescents' unique and common vulnerabilities and protective factors is essential for the development of appropriate interventions and programming focused on child and adolescent mental health. This paper examines the prevalence and predictors of depressive symptoms among high school adolescent girls in southern Uganda.

Methods: Baseline data from a longitudinal cluster randomized study involving 1260 adolescent girls (14-17 years), recruited from 47 secondary schools were utilized. Depressive symptoms were estimated using the 21-item Beck's Depression Inventory. Hierarchical linear regression modelling was utilized to estimate key predictors of depressive symptoms among adolescent girls.

Results: Of the total sample, 16.35% (n = 206) reported severe depressive symptoms and almost one in every three adolescent girls interviewed (29.68%, n = 374) reported moderate symptoms. These symptoms were more prevalent among older adolescents (16 years and above). In addition, family relationships, social support, as well as measures of psychological wellbeing (self-concept and self-esteem) were all associated with lower levels of depressive symptoms. Hopelessness was associated with higher levels of depressive symptoms among adolescent girls.

Conclusion: Findings from this study indicate a high prevalence of depressive symptoms, especially among older adolescent girls. In addition, family support factors and adolescents' psychological wellbeing were associated with low levels of depressive symptoms -pointing to the need to strengthen family functioning and adolescent's psychological wellbeing to mitigate risks. Taken together, findings support increasing calls for early screening and

detection of depressive symptoms to facilitate timely referral to care and treatment. Findings may also inform the development and incorporation of gender-specific mental health components in programming targeting adolescent girls, in low-resource communities in SSA.

Soc Psychiatry Psychiatr Epidemiol. 2021 Jan 4.
doi: 10.1007/s00127-020-02005-5. Online ahead of print.

Psychosocial interventions for self-harm in low-income and middle-income countries: systematic review and theory of change

Shilpa Aggarwal[1 2], George Patton[3], Michael Berk[4 5], Vikram Patel[6]

Abstract

Purpose: To synthesise the evidence on effectiveness, acceptability and the delivery mechanisms of psychosocial interventions for self-harm in low and middle income countries and to develop a pathway of change specific for self-harm interventions.

Method: Studies reporting one or more patient or implementation outcomes of a psychosocial intervention targeting self-harm and conducted in low- and middle-income countries were included. Taxonomy of treatment components and a theory of change map was created using information from the studies.

Results: We identified thirteen studies including nine randomised controlled trials (RCT), three non-RCTs, and a single experimental case design study. A single study using postcard contact and another using cognitive behaviour therapy (CBT) reported a reduction in self-harm attempts. Suicidal ideations were significantly reduced with CBT, volitional help sheets and postcard contact in different studies. Suicide risk assessment, problem solving and self-validation were the most frequently used elements in interventions. Goal-setting was the technique used most commonly. Cultural adaptations of psychotherapies were used in two studies. High attrition rates in psychotherapy trials, limited benefit of the delivery of treatment by non-specialist providers, and variable benefit observed using phone contact as a means to deliver intervention were other important findings.

Conclusion: There were no strong positive findings to draw definitive conclusions. Limited availability and evidence for culturally adapted interventions in self-harm, lack of evaluation of task sharing using evidence based interventions as well as a dearth in evaluation and reporting of various intervention delivery models in low- and middle-income countries were major literature gaps.

S Afr Med J. 2020 Dec 14;111(1):40-45.
doi: 10.7196/SAMJ.2020.v111i1.14520.

Substance use and depressive and anxiety symptoms among out-of-school adolescent girls and young women in Cape Town, South Africa

C P Bonner[1], T Carney, F A Browne, J W Ndirangu, B N Howard, W M Wechsberg

Abstract

Background: There is a high prevalence of substance use among youth in South Africa (SA), and adolescent girls and young women (AGYW) experience high rates of depression and anxiety. Substance use behaviours and mental health are associated with other public health problems among AGYW such as HIV and unintended pregnancy. Therefore, understanding

the relationship between substance use and mental health is imperative to improve AGYW's health.
Objectives: To examine the association between heavy drinking, marijuana, methamphetamine and methaqualone (Mandrax) use and depressive and anxiety symptoms among AGYW aged 16 - 19 years who have dropped out of school in Cape Town, SA.
Methods: Data for this report come from the baseline data of 500 participants of an ongoing cluster-randomised trial assessing the efficacy of a young woman-focused intervention to reduce substance use and HIV risk. After AGYW consented/assented to participate, they completed a urine drug screen and a baseline questionnaire.
Results: Logistic and negative binomial regressions, controlling for clustering at the neighbourhood level, revealed that frequency of depressive symptoms was significantly and positively related to a positive drug screen for Mandrax (β=0.07; p=0.03). All other associations between the frequency of depressive symptoms and substance use were not statistically significant (ps>0.05). The associations between frequency of anxiety symptoms and substance use were not statistically significant (ps>0.05).
Conclusions: Our findings highlight the need to address substance use, especially Mandrax use and its associated risk, and depression in an integrated, youth-friendly setting.

Violence Vict. 2020 Dec 1;35(6):861-884.
doi: 10.1891/VV-D-18-00060.
Reducing Physical Aggression in High School Students in KwaZulu-Natal: A Cluster Randomized Trial
Myra Taylor[1], Benn Sartorius[2], Saloshni Naidoo[2], Hein de Vries[3]
Youth violence is of public health and social concern. A South African cluster randomized trial (434 grade 10 students, 16 schools), used the Integrated Model for Behavior Change conceptual framework to implement a 20 module classroom-based intervention program. The study contributes to the literature and used a strong analytical technique since mixed effects linear regression assessed the impact of the intervention on physical violence endpoints and other socioeconomic confounders/factors. The intervention reduced students' experiencing physical violence compared to controls and social pressure for this, yet no differences were found for hitting others. Our results support findings that school programs against violence can reduce students' experience of physical violence, but translation of these findings to reduce the actual hitting of others may need further approaches and/or more time.

J Adolesc Health. 2021 May;68(5):914-921.
doi: 10.1016/j.jadohealth.2020.09.006. Epub 2020 Oct 21.
Nonverbal Response Cards Reduce Socially Desirable Reporting of Violence Among Adolescents in Rural Burkina Faso: A Randomized Controlled Trial
Guy Harling[1], Mamadou Bountogo[2], Ali Sié[2], Till Bärnighausen[3], David P Lindstrom[4]
Abstract
Purpose: Accurate measures of violence are difficult to obtain from self-reported data because of stigmatization and social undesirability of the topic. Most methods that attempt

to reduce such biases require literacy and either remove the benefits of interviewer guidance or do not give individual-level results. We tested a low-tech nonverbal response card that avoids revealing interviewees' responses to interviewers while retaining interviewer support among adolescents in communities with very low educational attainment.
Methods: As part of a broader health questionnaire, we asked a sample of 1,644 adolescents, aged 12-20 years, in northwestern Burkina Faso about their experiences of physical and sexual violence. We randomized participants to either a conventional verbal response arm or a nonverbal response card arm where respondents' answers were unspoken and not displayed to interviewers. We first evaluated response validity and reliability in each arm, then compared prevalence rates across arms and evaluated whether any differences varied by respondent characteristics using regression models.
Results: The level of internal reliability of responses among nonverbal respondents was similar to or greater than that of verbal respondents. Nonverbal respondents reported similar patterns of physical assault and sexual debut as verbal respondents but significantly higher levels of sexual assault and forced sex. These differences were broadly similar across sample subgroups defined by age, gender, proneness to social desirability, and mental health.
Conclusions: Nonverbal response cards offer a practical and beneficial method for reducing underreporting of stigmatized and traumatic experiences while maintaining data quality in low-literacy populations.

Adolescent HIV prevention and treatment

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doi: 10.1007/s10461-020-02812-6.

Social and Economic Equity and Family Cohesion as Potential Protective Factors from Depression Among Adolescents Living with HIV in Uganda

Patricia Cavazos-Rehg[1], Christine Xu[2 3], Erin Kasson[2], William Byansi[3], Ozge Sensoy Bahar[3], Fred M Ssewamala[3]

Abstract
Adolescents living with HIV in Uganda are impacted by poverty and face a number of health and social challenges including access to medication, health complications, and social stigma. These stressors have been linked to depression, which can lead to lower HIV treatment adherence. This study seeks to determine how social and economic equity, family cohesion, and social supports may be related to depression among adolescents living with HIV. We used baseline data from the Suubi + Adherence study, a 5-year longitudinal randomized controlled trial among adolescents living with HIV in southwestern Uganda (n = 675; ages 10-16 years). Hierarchical logistic regression models were conducted separately among in-school adolescents and out-of-school adolescents to assess the hypothesized associations between economic and social equity, social support, and depression. About half of the participants meet the criteria for depression. Adolescents with depression were found to have fewer economic and social supports. Our findings indicate that social and economic equity [odds ratio (OR) = 0.85, 95% confidence interval (CI) 0.74, 0.99], family cohesion (OR =

0.94, 95% CI 0.91-0.96), and social support from friends (OR = 0.95, 95% CI 0.91-0.998) are associated with depression for in-school HIV infected adolescents and could be protective factors. The results of this study suggest that social and economic equity may play a protective role against depression and other poor mental health outcomes. Potential interventions for adolescents living with HIV should consider these social and familial factors as they may be protective of depression in this population.

AIDS Behav. 2021 May 7.
doi: 10.1007/s10461-021-03237-5. Online ahead of print.

A Pilot RCT Evaluating InThistoGether, an mHealth HIV Prevention Program for Ugandan Youth

Michele L Ybarra[1], Edgar Agaba[2], Novatus Nyemara[2 3]

Abstract

Despite data suggesting that older adolescence is an important period of risk for HIV acquisition in Uganda, tailored HIV prevention programming is lacking. To address this gap, we developed and tested nationally, InThistoGether (ITG), a text messaging-based HIV prevention program for 18-22 year-old Ugandan youth. To assess feasibility and acceptability, and preliminary indications of behavior change, a randomized controlled trial was conducted with 202 youth. Participants were assigned either to ITG or an attention-matched control group that promoted general health (e.g., self-esteem). They were recruited between December 2017 and April 2018 on Facebook and Instagram, and enrolled over the telephone. Between 5-10 text messages were sent daily for seven weeks. Twelve weeks later, the intervention ended with a one-week 'booster' that reviewed the main program topics. Measures were assessed at baseline and intervention end, 5 months post-randomization. Results suggest that ITG is feasible: The retention rate was 83%. Ratings for the content and program features met acceptability thresholds; program experience ratings were mixed. ITG also was associated with significantly higher rates of condom-protected sex (aIRR = 1.68, p < 0.001) and odds of HIV testing (aOR = 2.41, p = 0.03) compared to the control group. The odds of abstinence were similar by experimental arm however (aOR = 1.08, p = 0.86). Together, these data suggest reason for optimism that older adolescent Ugandans are willing to engage in an intensive, text messaging-based HIV prevention programming. Given its wide reach and low cost, text messaging should be better utilized as an intervention delivery tool in low-income settings like Uganda. Findings also suggest that ITG may be associated with behavior change in the short-term. (Trial registration: ClinicalTrials.gov ID# NCT02729337).

J Int AIDS Soc. 2020 Sep;23 Suppl 5(Suppl 5):e25563.
doi: 10.1002/jia2.25563.

"If it is left, it becomes easy for me to get tested": Use of oral self-tests and community health workers to maximize the potential of home-based HIV testing among adolescents in Lesotho

Alain Amstutz[1 2 3], Mathebe Kopo[4], Thabo I Lejone[4], Lefu Khesa[4], Mpho Kao[4], Josephine Muhairwe[4], Tracy R Glass[1 2], Niklaus D Labhardt[1 2 3]

Abstract

Introduction: Home-based HIV testing fails to reach high coverage among adolescents and young adults (AYA), mainly because they are often absent during the day of home-based testing. ADORE (ADolescent ORal tEsting) is a mixed-method nested study among AYA in rural Lesotho, measuring the effect of home-based secondary distribution of oral HIV self-tests (HIVST) on coverage, as well as exploring how AYA perceive this HIV self-testing model.
Methods: ADORE study was nested in a cluster-randomized trial. In intervention village-clusters, oral HIVST were left for household members who were absent or declined testing during a testing campaign. One present household member was trained on HIVST use. Distributed HIVST were followed up by village health workers (VHW). In control clusters no self-tests were distributed. The quantitative outcome was testing coverage among AYA (age 12 to 24) within 120 days, defined as a confirmed HIV test result or known status, using adjusted random-effects logistic regression on the intention-to-treat population. Qualitatively, we conducted in-depth interviews among both AYA who used and did not use the distributed HIVST.
Results: From July 2018 to December 2018, 49 and 57 villages with 1471 and 1620 consenting households and 1236 and 1445 AYA in the control and intervention arm, respectively, were enrolled. On the day of the home-visit, a testing coverage of 37% (461/1236) and 41% (596/1445) in the control and the intervention arm, respectively, were achieved. During the 120 days follow-up period, an additional 23 and 490 AYA in control and intervention clusters, respectively, knew their status. This resulted in a testing coverage of 484/1236 (39%) in the control versus 1086/1445 (75%) in the intervention arm (aOR 8.80 [95% CI 5.81 to 13.32]; $p < 0.001$). 21 interviews were performed. Personal assistance after the secondary distribution emerged as a key theme and VHWs were generally seen as a trusted cadre.
Conclusions: Secondary distribution of HIVST for AYA absent or refusing to test during home-based testing in Lesotho resulted in an absolute 36% increase in coverage. Distribution should, however, go along with clear instructions on the use of the HIVST and a possibility to easily access more personal support.

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Prevalence and characteristics of HIV drug resistance among antiretroviral treatment (ART) experienced adolescents and young adults living with HIV in Ndola, Zambia

Sam Miti[1,2], Ray Handema[2], Lloyd Mulenga[3,4,5], Jonathan K Mwansa[1], Elizabeth Abrams[6], Christiana Frimpong[1], Virginia M Burke[6], Mangani Zulu[1], Mpanji Siwingwa[3], David Mwakazanga[2], Sam Kalibala[7], Julie A Denison[6]

Abstract
Background: HIV drug resistance (HIVDR) poses a threat to the HIV epidemic control in Zambia especially in sub-populations such as the 15-24 years where there is poor virological suppression. Understanding the prevalence and patterns of HIVDR in this population (15-24 years) will contribute to defining effective antiretroviral therapy (ART) regimens, improving clinical decision making, and supporting behavioral change interventions needed to achieve HIV epidemic control.
Methods: A cross-sectional analysis of study enrollment data from the Project YES! Youth Engaging for Success randomized controlled trial was conducted. Participants were 15 to 24 years old, who knew their HIV status, and had been on ART for at least 6 months. All

participants completed a survey and underwent viral load (VL) testing. Participants with viral failure (VL ≥1,000 copies/mL) underwent HIVDR testing which included analysis of mutations in the protease and reverse transcriptase genes.
Results: A total of 99 out of 273 analyzed participants receiving ART had VL failure, of whom 77 had successful HIVDR amplification and analysis. Out of the 77, 75% (58) had at least one drug resistant mutation, among which 83% (48/58) required a drug change. Among the 58 with HIVDR mutations, the prevalence of at least one HIVDR mutation to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) were 81%, 65.5% and 1.7%. The mutation M184V which confers resistance to NRTI drugs of lamivudine (3TC) and emtricitabine (FTC) was the most common (81%) among NRTI associated mutations followed by K65R (34.5%) which is associated with both tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF) resistance. Thymidine analogue mutations (TAMs) which confer resistance primarily to zidovudine (AZT), stavudine (d4T) and other NRTIs were observed at 32.8%. Common TAMs were K70RTQNE (32.8%), K219QE (22.4%), D67N (17.2%) and T215IT (15.5%). The most common NNRTI associated mutation was the K103N (65.5%) which confers resistance to both efavirenz (EFV) and nevirapine (NVP). There was a relatively high occurrence of other NNRTI mutations V106A (36.2%), as well as Y188C (36.2%) and Y181C (36.2%) which confer resistance to etravirine.
Conclusions: There is a high prevalence of HIVDR including TAMs despite majority of these patients (90.48%) being on AZT or d4T sparing first line ART among the youth. Emergence of these mutations including the NNRTI associated mutations (Y181C and Y188C) may compromise future second- and third-line regimens in the absence of routine HIVDR testing. HIVDR monitoring at start of ART or at first-line failure can better inform clinical decision making and ART programing.

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HIV Care Cascade Among Adolescents in a "Test and Treat" Community-Based Intervention: HPTN 071 (PopART) for Youth Study
Kwame Shanaube[1], David Macleod[2], Mwate Joseph Chaila[3], Constance Mackworth-Young[4], Graeme Hoddinott[5], Ab Schaap[6], Sian Floyd[2], Peter Bock[5], Richard Hayes[2], Sarah Fidler[7], Helen Ayles[8]
Abstract
Purpose: The PopART for Youth (P-ART-Y) study was nested within the HPTN 071 (PopART) trial, a three-arm community randomized trial in 21 communities in Zambia and South Africa. The P-ART-Y study evaluated the acceptability and uptake of a combination HIV prevention package among young people. We report on the HIV care cascade for adolescents aged 10-19 years from 14 communities receiving the full HIV prevention package in Zambia and South Africa.
Methods: Adolescents were offered participation in the PopART intervention, which included universal home-based HIV testing, linkage to care, antiretroviral therapy (ART) adherence, and other services. Data were collected from September 2016 to December 2017, covering the third round (R3) of the intervention.

Results: We enumerated (listed) 128,241 adolescents (Zambia: 95,295 and South Africa: 32,946). Of the adolescents offered HIV testing, 81.9% accepted in Zambia and 70.3% in South Africa. Knowledge of HIV status was higher among older adolescents and increased from 31.4% before R3 to 88.3% at the end of R3 in Zambia and from 28.3% to 79.5% in South Africa. Overall, there were 1,710 (1.9%) adolescents identified as living with HIV by the end of R3 (515 new diagnoses and 1,195 self-reported). Of the new diagnoses, 335 (65.0%) were girls aged 15-19 years. The median time to initiate ART was 5 months. ART coverage before and after R3 increased from 61.3% to 78.7% in Zambia and from 65.6% to 87.8% in South Africa, with boys having higher uptake than girls in both countries.
Conclusions: The PopART intervention substantially increased coverage toward the first and second UNAIDS 90-90-90 targets in adolescents.

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The efficacy and cost-effectiveness of a family-based economic empowerment intervention (Suubi + Adherence) on suppression of HIV viral loads among adolescents living with HIV: results from a Cluster Randomized Controlled Trial in southern Uganda

Yesim Tozan[1], Ariadna Capasso[1], Sicong Sun[2 3], Torsten B Neilands[4], Christopher Damulira[5], Flavia Namuwonge[5], Gertrude Nakigozi[6], Abel Mwebembezi[5 7], Barbara Mukasa[8], Ozge Sensoy Bahar[2 3], Proscovia Nabunya[2 3], Claude A Mellins[9], Mary M McKay[2], Fred M Ssewamala[2 3]

Abstract
Introduction: Evidence from low-resource settings indicates that economic insecurity is a major barrier to HIV treatment adherence. Economic empowerment (EE) interventions have the potential to improve adherence outcomes among adolescents living with HIV (ALWHIV) by mitigating the effects of poverty. This study aims to assess the efficacy and cost-effectiveness of a savings-led family-based EE intervention, Suubi + Adherence, aimed at improving antiretroviral therapy (ART) adherence outcomes ALWHIV in Uganda.
Methods: Adolescents (mean age 12 years at enrolment; 56% female) receiving ART for HIV at 39 health centres were randomized to Suubi + Adherence intervention (n = 358) or bolstered standard of care (BSOC; n = 344). A difference-in-differences analysis was employed to assess the change in the proportion of virally suppressed adolescents (HIV RNA viral load <40 copies/mL) over 24 months. The cost-effectiveness analysis examined how much the intervention cost to virally suppress one additional adolescent relative to BSOC from the healthcare provider perspective.
Results: At 24 months, the intervention was associated with an 8.85-percentage point [95% confidence interval (CI) 0.80 to 16.90 percentage points] increase in the proportion of virally suppressed adolescents between the study arms (p = 0.032). Per-participant costs were US$177 and US$263 for the BSOC and intervention groups respectively. The incremental cost of virally suppressing one additional adolescent was estimated at US$970 [95% CI, US$508 to 10,725] over two years.
Conclusions: Our results support the integration of family-based EE interventions into adherence-support strategies as part of routine HIV care in low-resource settings to address the underlying economic drivers of poor ART adherence among ALWHIV. Moreover, per-participant costs to achieve viral suppression do not seem prohibitive compared to other

community-based adherence interventions targeted at ALWHIV in low-resource settings. Further research on combination interventions at the nexus of economic security and HIV treatment and care is needed to inform the development of feasible and scalable HIV policies and programmes.

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Effects of vitamin D and calcium supplementation on bone mineral density among Thai youth using daily HIV pre-exposure prophylaxis

Krittaporn Pornpaisalsakul[1,2], Wipaporn Natalie Songtaweesin[2], Supatporn Tepmongkol[3,4], Prissana Wongharn[2], Surinda Kawichai[2], Vichit Suponsilchai[1,5], Suvaporn Anugulruengkitt[1,2], Thanyawee Puthanakit[1,2], CE-PID - IHRI Adolescent Study Team

Abstract

Introduction: Tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) is used for HIV pre-exposure prophylaxis (PrEP). TDF may affect bone mineral density (BMD), particularly in youth who are at a stage of peak bone mass accrual. The objective of this study was to evaluate the effect of vitamin D and calcium supplementation on BMD among Thai youth receiving daily oral PrEP.

Methods: This open-label randomized trial was conducted in male youth aged between 15 and 24 years. Participants were randomized to Arm A who received once-daily TDF/FTC plus vitamin D3 and calcium supplementation with meals twice daily (400 units of vitamin D3 and 1200 mg of elemental calcium/day) or Arm B who received once-daily TDF/FTC only. PrEP users were defined as taking at least two tablets/week (tenofovir-diphosphate level of >350 fmol/punch). Adherence to vitamin D/calcium supplementation was defined as self-reported adherence of >50%. Lumbar spine (L2-L4) BMD (LSBMD) was evaluated by dual-energy X-ray absorptiometry scan zero and six months after PrEP initiation.

Results: From March 2019 to March 2020, 100 youth were enrolled. Baseline characteristics between the two arms were similar. Median (IQR) age was 18 (17 to 20) years. At entry, median (IQR) LSBMD z-score was -0.8 (-1.5 to -0.3), 17% had low LSBMD (Z-score < -2). The median amount of calcium intake from nutritional three-day recall was 167 (IQR 94 to 272) mg/day, 39% of participants had vitamin D deficiency, defined as 25(OH)D levels <20 IU/mL. At six months, 79 participants were evaluated. Of these, 42 (52%) were PrEP takers and 25 of 38 (66%) of arm A participants had good adherence to vitamin D/calcium supplementation. Significantly higher proportions of youth in arm A compared to arm B had >3% increase in LSBMD at month 6 compared to baseline (67.6% vs. 42.9% respectively; p = 0.03). There were significantly higher increases in LSBMD among youth with vitamin D deficiency who were supplemented; arm A + 0.05 (0 to 0.05) compared to arm B + 0.03 (-0.1 to 0.03), p = 0.04.

Conclusions: Increases in LSBMD over six months among youth using PrEP who received vitamin D/calcium supplementation was greater than those not supplemented. Long-term follow-up should be considered to explore long-term outcomes.

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A group-based mental health intervention for young people living with HIV in Tanzania: results of a pilot individually randomized group treatment trial

Dorothy E Dow[1 2 3], Blandina T Mmbaga[4 5], John A Gallis[4 6], Elizabeth L Turner[4 6], Monica Gandhi[7], Coleen K Cunningham[8 4], Karen E O'Donnell[9 10]

Abstract

Background: Increasing numbers of young people living with HIV (YPLWH) have unaddressed mental health challenges. Such challenges are associated with poor antiretroviral therapy (ART) adherence and high mortality. Few evidence-based mental health interventions exist to improve HIV outcomes among YPLWH.

Methods: This pilot group treatment trial individually randomized YPLWH from two clinical sites in Tanzania, evaluated acceptability, feasibility, and preliminary effectiveness of a mental health intervention, Sauti ya Vijana (SYV; The Voice of Youth), was compared to the local standard-of-care (SOC) for improving ART adherence and virologic suppression. Enrolled YPLWH were 12-24 years of age and responded to mental health and stigma questionnaires, self-reported adherence, objective adherence measures (ART concentration in hair), and HIV RNA at baseline and 6-months (post-intervention). Feasibility and acceptability were evaluated, and potential effectiveness was assessed by comparing outcomes between arms using mixed effects modeling.

Results: Between June 2016 and July 2017, 128 YPLWH enrolled; 105 were randomized and 93 (55 in SYV) followed-up at 6-months and were thereby included in this analysis. Mean age was 18.1 years; 51% were female; and 84% were HIV-infected perinatally. Attendance to intervention sessions was 86%; 6-month follow-up was 88%, and fidelity to the protocol approached 100%. Exploratory analyses of effectiveness demonstrated self-reported adherence improved by 7.3 percentage points (95% CI: 2.2, 12.3); and the pooled standard deviation for all ART concentration values increased by 0.17 units (95% CI: - 0.52, 0.85) in the SYV arm compared to SOC. Virologic suppression rates (HIV RNA < 400 copies/mL) at baseline were 65% in both arms but increased to 75% in the SYV arm while staying the same in the SOC arm (RR 1.13; 95% CI: 0.94, 1.36).

Conclusions: YPLWH often have poor HIV outcomes, making interventions to improve outcomes in this population critical. This pilot trial of the Tanzania-based SYV intervention demonstrated trends towards improvement in ART adherence and virologic outcomes among YPLWH, supporting efforts to scale the intervention into a fully-powered effectiveness trial.

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Family Connections randomized controlled trial: assessing the feasibility and acceptability of an intervention with adolescents living with HIV and their caregivers in Ndola, Zambia

Julie A Denison[1], Catherine Packer[2], Namakau Nyambe[3], Rebecca B Hershow[2], Stephanie Caldas[1], Sam Miti[4], Swati Sudarsan[1], Mario Chen[5], Alissa Bernholc[5], Jonathan K Mwansa[4], Donna R McCarraher[2]

Abstract

Achieving the 95-95-95 UNAIDS targets requires meeting the needs of adolescents, however we lack evidenced-based approaches to improving adolescent adherence to antiretroviral therapy (ART), increasing viral suppression, and supporting general wellbeing. We developed *Family Connections* as a group intervention for adolescents and their adult caregivers and conducted a randomized controlled trial in Ndola, Zambia to test feasibility and acceptability. Fifty pairs (*n* = 100) of adolescents (15-19 years and on ART ≥ 6 months) and their caregivers were randomly assigned either to the intervention consisting of 10 group sessions over 6 months, or to a comparison group, which received the usual care. Each pair completed baseline and endline surveys, with adolescents also undergoing viral load testing. Of the 24-intervention adolescent/caregiver pairs, 88% attended at least eight group sessions. Most adolescents (96%) and all caregivers would recommend *Family Connections* to peers. Adolescent viral failure decreased but did not significantly differ by study group. Adolescents in the intervention group showed a greater reduction in HIV-related feelings of worthlessness and shame than the comparison group. The feasibility, acceptability, and the positive trend toward significantly reducing internalized stigma, generated by this *Family Connections* pilot study, contributes valuable data to support adolescent/caregiver approaches that use peer groups.

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Impact of a community-wide combination HIV prevention intervention on knowledge of HIV status among adolescents

Kwame Shanaube[1], Ab Schaap[1 2], Graeme Hoddinott[3], Constance Mubekapi-Musadaidzwa[3], Sian Floyd[2], Peter Bock[3], Richard Hayes[2], Sarah Fidler[4], Helen Ayles[1 2], HPTN 071 (PopART) Study Team

Abstract

Objective: To determine the impact of a community-wide combination HIV-prevention package (PopART Intervention) that includes universal testing and treatment (UTT) on knowledge of HIV status, among adolescents aged 15--19 years.

Design: The HPTN 071 (PopART) for Youth (P-ART-Y) study was nested within HPTN 071 (PopART), a three-arm, cluster-randomized trial conducted from 2013 through 2018 in 21 communities in Zambia and South Africa. Communities were randomly assigned to arm A (combination prevention intervention with universal ART), arm B (prevention intervention with ART provided according to local guidelines), or arm C (standard-of-care).

Methods: Knowledge of HIV status was measured using data collected during the third round of the PopART intervention in arms A and B (October 2016 to December 2017) and by conducting a cross-sectional survey (August to November 2017) in arm C communities to provide comparative data. The survey was conducted among ~200 randomly selected adolescents in each community. We used linear regression of the 21 community-level values to make comparisons among trial arms.

Results: Knowledge of HIV status was 78.2% (23 544/30 089) in arm A and 76.0% (24 417/32 148) in arm B communities, compared with 32.9% (698/2120) in arm C communities. Knowledge of HIV status varied by country, triplet, sex, and age. The adjusted mean difference was 42.3% between arm A with arm C, 95% CI 28.1-56.6, P less than 0.001 and 40.4% between arm B with arm C, 95% CI 24.6-56.2, P < 0.001).
Conclusion: Implementation of a community-wide combination HIV-prevention package that includes UTT substantially enhanced knowledge of HIV status among adolescents.

Am J Public Health. 2021 Mar;111(3):504-513.
doi: 10.2105/AJPH.2020.306044. Epub 2021 Jan 21.

Impact of a Family Economic Intervention (Bridges) on Health Functioning of Adolescents Orphaned by HIV/AIDS: A 5-Year (2012-2017) Cluster Randomized Controlled Trial in Uganda

Fred M Ssewamala[1], Julia Shu-Huah Wang[1], Rachel Brathwaite[1], Sicong Sun[1], Larissa Jennings Mayo-Wilson[1], Torsten B Neilands[1], Jeanne Brooks-Gunn[1]

Abstract

Objectives. To investigate the long-term impacts of a family economic intervention on physical, mental, and sexual health of adolescents orphaned by AIDS in Uganda.**Methods.** Students in grades 5 and 6 from 48 primary schools in Uganda were randomly assigned at the school level (cluster randomization) to 1 of 3 conditions: (1) control (n = 487; 16 schools), (2) Bridges (1:1 savings match rate; n = 396; 16 schools), or (3) Bridges PLUS (2:1 savings match rate; n = 500; 16 schools).**Results.** At 24 months, compared with participants in the control condition, Bridges and Bridges PLUS participants reported higher physical health scores, lower depressive symptoms, and higher self-concept and self-efficacy. During the same period, Bridges participants reported lower sexual risk-taking intentions compared with the other 2 study conditions. At 48 months, Bridges and Bridges PLUS participants reported better self-rated health, higher savings, and lower food insecurity. During the same period, Bridges PLUS participants reported reduced hopelessness, and greater self-concept and self-efficacy. At 24 and 48 months, Bridges PLUS participants reported higher savings than Bridges participants.**Conclusions.** Economic interventions targeting families raising adolescents orphaned by AIDS can contribute to long-term positive health and overall well-being of these families.

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The Impact of a Family-Based Economic Intervention on the Mental Health of HIV-Infected Adolescents in Uganda: Results From Suubi + Adherence

Patricia Cavazos-Rehg[1], William Byansi[2], Christine Xu[3], Proscovia Nabunya[2], Ozge Sensoy Bahar[2], Jacob Borodovsky[4], Erin Kasson[4], Nnenna Anako[3], Claude Mellins[5], Christopher Damulira[6], Torsten Neilands[7], Fred M Ssewamala[2]

Abstract

Purpose: This study examines the extent to which three mental health measures (hopelessness, depression, and poor self-concept) are improved through a family-based economic intervention implemented among adolescents living with HIV in Uganda.
Methods: We used repeated measures from Suubi + Adherence, a large-scale 6-year (2012-2018) longitudinal randomized controlled trial. Bivariate analyses were conducted to test for observable group differences between the intervention and control conditions. Multilevel piecewise repeated measure mixed models were then conducted to assess hypothesized time × intervention interaction in changes in hopelessness, depression, and self-concept using participant-specific follow-up intervals.
Results: At 24-month postintervention initiation, adolescents in the intervention condition reported a statistically significant lower hopelessness score than adolescents in the control condition (4.79 vs. 5.56; p = .018; N = 358). At 36-month follow-up, the intervention condition reported a statistically significant lower score on depression in the depression subgroup (N = 344) than the control condition (4.94 vs. 5.81; p = .029).
Conclusions: The results indicate that family-based economic interventions such as Suubi + Adherence can effectively improve the mental health of adolescents living with HIV who evidenced mental health challenges at baseline. Given the promising positive effects of these interventions, at least in the short term, future studies should investigate strategies to promote the sustainability of these mental health benefits.

Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

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Efficacy of processed amaranth-containing bread compared to maize bread on hemoglobin, anemia and iron deficiency anemia prevalence among two-to-five year-old anemic children in Southern Ethiopia: A cluster randomized controlled trial

Alemselam Zebdewos Orsango[1,2], Eskindir Loha[1,2], Bernt Lindtjørn[1,2], Ingunn Marie S Engebretsen[2]

Abstract
Background: Few studies have evaluated iron-rich plant-based foods, such as amaranth grain, to reduce anemia and iron deficiency anemia. Amaranth is rich in nutrients, but with high level of phytate. The objective of this trial was to evaluate the efficacy of home processed amaranth grain containing bread in the treatment of anemia, hemoglobin concentration and iron deficiency anemia among two-to-five year-old children in Southern Ethiopia.
Method: Children with anemia (hemoglobin concentration <110.0g/L) (N = 100) were identified by random sampling and enrolled in a 1:1 cluster randomized controlled trial for six months in 2017. The amaranth group (N = 50), received 150g bread containing 70% amaranth and 30% chickpea, the amaranth grain was processed at home (soaking, germinating, and fermenting) to decrease the phytate level. The maize group (N = 50),

received 150g bread, containing processed maize (roasted and fermented) to give a similar color and structure with amaranth bread. Hemoglobin, ferritin, and CRP were measured at baseline and at the end of intervention. Hemoglobin and ferritin values were adjusted for altitude and infection, respectively. Generalized estimating equation and generalized linear model were used to analyze the data.
Result: In the last follow-up measure anemia prevalence was significantly lower in the amaranth group (32%) as compared with the maize group (56%) [adjusted risk ratios, aRR: 0.39 (95%CI: 0.16-0.77)]. Hemoglobin concentration estimate of beta coefficient was significantly higher in the amaranth group compared with the maize group [aβ 8.9g/L (95%CI: 3.5-14.3)], p-value <0.01. The risk of iron deficiency anemia is significantly lower in the amaranth group [aRR: 0.44 (95%CI: 0.23-0.83)] in the intention to treat analysis but not significant in the complete case analysis. There was no significant difference between groups in iron deficiency [aRR: 0.81 (95%CI: 0.55-1.19)].
Conclusion: Processed amaranth bread had favorable effects on hemoglobin concentration and has the potential to minimize anemia prevalence.

Am J Clin Nutr. 2021 May 8;113(5):1104-1114.
doi: 10.1093/ajcn/nqaa417.
Antenatal iron supplementation, FGF23, and bone metabolism in Kenyan women and their offspring: secondary analysis of a randomized controlled trial
Vickie S Braithwaite[1,2], Martin N Mwangi[3,4], Kerry S Jones[5], Ayşe Y Demir[6], Ann Prentice[1,7], Andrew M Prentice[7], Pauline E A Andang'o[8], Hans Verhoef[3,9]
Abstract
Background: Fibroblast growth factor-23 (FGF23) regulates body phosphate homeostasis primarily by increasing phosphaturia. It also acts as a vitamin D-regulating hormone. Maternal iron deficiency is associated with perturbed expression and/or regulation of FGF23 and hence might be implicated in the pathogenesis of hypophosphatemia-driven rickets in their offspring.
Objectives: We aimed to determine the effect of antenatal oral iron supplementation on FGF23 concentration and maternal and infant markers of bone-mineral regulation.
Methods: We performed a secondary analysis of a trial in which 470 rural Kenyan women with singleton pregnancies and hemoglobin concentrations ≥ 90 g/L were randomly allocated to daily, supervised supplementation with 60 mg elemental iron as ferrous fumarate or placebo from 13-23 weeks of gestation until 1 mo postpartum. As previously reported, iron supplementation improved iron status in mothers and neonates. For the present study, we reanalyzed all available plasma samples collected in mothers and neonates at birth, with primary outcomes being concentrations of FGF23, measured by 2 assays: 1 that detects intact hormone and C-terminal cleavage products (total-FGF23) and another that detects the intact hormone only (intact-FGF23).
Results: Analysis was performed on 433 women (n = 216, iron group; n = 217, placebo group) and 414 neonates (n = 207, iron group; n = 207, placebo group). Antenatal iron supplementation reduced geometric mean total-FGF23 concentrations in mothers and neonates by 62.6% (95% CI: 53.0%, 70.3%) and 15.2% (95% CI: -0.3%, 28.4%, P = 0.06), respectively. In addition, it increased geometric mean neonatal intact-FGF23 concentrations

by 21.6% (95% CI: 1.2%, 46.1%), increased geometric mean maternal hepcidin concentrations by 136.4% (95% CI: 86.1%, 200.3%), and decreased mean maternal 25-hydroxyvitamin D concentrations by 6.1 nmol/L (95% CI: -11.0, -1.2 nmol/L).
Conclusions: Analysis of this randomized trial confirms that iron supplementation can reverse elevated FGF23 production caused by iron deficiency in iron-deficient mothers and their neonates. Further investigations are warranted to assess to what extent iron supplementation can prevent FGF23-mediated hypophosphatemic rickets or osteomalacia.

Ann N Y Acad Sci. 2021 May;1492(1):82-95.
doi: 10.1111/nyas.14556. Epub 2020 Dec 31.
Guava with an institutional supplementary meal improves iron status of preschoolers: a cluster-randomized controlled trial
Dripta Roy Choudhury[1], Madhavan Nair Krishnapillai[2], Balakrishna Nagalla[3], Radhakrishna Vijaya Kankipati[4], Sudip Ghosh[1], Jagdish Buwade[5], Sylvia Fernandez-Rao[5]
Abstract
The Integrated Child Development Services of India provides Supplementary Nutrition Program (SNP) to preschoolers. Using this platform, the current study examined the impact of diversifying a cereal/pulse-based SNP-meal with guava on iron status and cognitive development among 24-48 months old children. A three-arm, nonblinded, cluster-randomized controlled trial (CTRI/2014/09/004983) included 399 beneficiaries from 28 preschools in 16 villages in Telangana state, India. The villages were randomly assigned to receive 25 g of guava (guava group (GG)), banana (banana group (BG)), or cucumber (cucumber group (CG)) along with a SNP meal for 140 days. Nutrient biomarkers (iron status, plasma vitamin C, vitamin B_{12} , and folate), cognitive development, anthropometric indicators (WAZ, HAZ, and WHZ), and morbidity were assessed at baseline and endline. A linear mixed model and a generalized estimating equation were applied to compare changes in outcomes across the groups. All outcome variables were comparable across groups at baseline. The iron to vitamin C molar ratio improved in the GG from 1:1.4 to 1:12 but remained unaltered in control groups. Higher hemoglobin ($P = 0.002$), serum ferritin (SF; $P < 0.001$), vitamin C ($P = 0.047$), and lower soluble transferrin receptor (sTfR; $P < 0.001$) causing decreased prevalence of iron deficiency (ID) ($P = 0.003$) were observed in the GG compared with BG and CG. Prevalence of acute respiratory infection (ARI) was lower in the GG ($P = 0.035$) versus controls. No impact was observed on cognitive development or growth. Thus, diversifying a cereal/pulse-based meal with guava increased meal vitamin C content, thereby reducing ID and ARI-related morbidity. This approach represents a valid and scalable strategy to address ID among young children.

Patient Educ Couns. 2021 May 3;S0738-3991(21)00297-4.
doi: 10.1016/j.pec.2021.04.032. Online ahead of print.
Improving iron folic acid consumption through interpersonal communication: Findings from the Reduction in Anemia through Normative Innovations (RANI) project

Rohini Ganjoo[1], Rajiv N Rimal[2], Sameera A Talegawkar[3], Erica Sedlander[4], Ichhya Pant[5], Jeffrey B Bingenheimer[5], Shikha Chandarana[5], Aika Aluc[5], Yichen Jin[3], Hagere Yilma[5], Bikash Panda[6]

Abstract

Objective: More than half of Indian women of reproductive age are anemic. Regular iron folic acid uptake can prevent and treat anemia. This study investigated the effect of interpersonal communication on improving IFA use among women of reproductive age.

Methods: The Reduction in Anemia through Normative Innovations (RANI) Project is a cluster randomized trial that collected longitudinal data from control (n = 1896) and intervention (n = 1898) communities in Odisha, India at Time 1 and six months later at Time 2. Structural equation models assessed the effect of the intervention on iron folic acid use via multiple interpersonal communication pathways.

Results: Compared to the control arm, iron folic acid use significantly increased in the intervention arm. Both, general health interpersonal communication and anemia-specific interpersonal communication were augmented in the intervention communities. The impact of the intervention on iron folic acid use was mediated through anemia-specific interpersonal communication.

Conclusion: The RANI Project increased interpersonal communication among participants, resulting in increased iron folic acid use for anemia reduction.

Practice implications: Strategic use of targeted interpersonal communication to promote behavior change appears to be a viable strategy to increase iron folic acid use to reduce anemia.

J Nutr. 2020 Dec 10;150(12):3200-3207.
doi: 10.1093/jn/nxaa226.

Iron Absorption is Greater from Apo-Lactoferrin and is Similar Between Holo-Lactoferrin and Ferrous Sulfate: Stable Iron Isotope Studies in Kenyan Infants

Nadja Mikulic[1], Mary A Uyoga[1], Edith Mwasi[2], Nicole U Stoffel[1], Christophe Zeder[1], Simon Karanja[3], Michael B Zimmermann[1]

Abstract

Background: Whether lactoferrin (Lf) binds iron to facilitate its absorption or to sequester iron from potential enteropathogens remains uncertain. Bovine Lf is added to many infant formulas, but previous studies in infants reported that Lf had no effect on or inhibited iron absorption. The effects of the apo (iron-free) or the holo (iron-loaded) forms of Lf on iron absorption are unclear.

Objectives: Our objective was to compare iron absorption from a maize-based porridge containing: 1) labeled ferrous sulfate (FeSO4) alone; 2) labeled FeSO4 given with bovine apo-Lf; and 3) intrinsically labeled bovine holo-Lf.

Methods: In a crossover study, we measured iron absorption in Kenyan infants (n = 25; mean ± SD age 4.2 ± 0.9 months; mean ± SD hemoglobin 109 ± 11 g/L) from maize-based test meals containing: 1) 1.5 mg of iron as 54Fe-labeled FeSO4; 2) 1.42 mg of iron as 58Fe-labeled FeSO4, given with 1.41 g apo-Lf (containing 0.08 mg iron); and 3) 1.41 g holo-Lf carrying 1.5 mg iron as 57Fe. The iron saturation levels of apo- and holo-Lf were 0.56% and 47.26%, respectively primary outcome was fractional iron absorption (FIA), assessed by erythrocyte incorporation of isotopic labels.

Results: The FIA from the meal containing apo-Lf + FeSO4 (geometric mean, 9.8%; -SD and +SD, 5.4% and 17.5%) was higher than from the meals containing FeSO4 (geometric mean, 6.3%; -SD and +SD, 3.2% and 12.6%; P = 0.002) or holo-Lf (geometric mean, 5.0%; -SD and +SD, 2.8% and 8.9%; P <0.0001). There was no significant difference in FIA when comparing the meals containing holo-Lf versus FeSO4 alone (P = 0.24).
Conclusions: The amount of iron absorbed from holo-Lf was comparable to that of FeSO4, and the addition of apo-Lf to a test meal containing FeSO4 significantly increased (+56%) iron absorption. These findings suggest that Lf facilitates iron absorption in young infants. Because Lf binds iron with high affinity, it could be a safe way to provide iron to infants in low-income countries, where iron fortificants can adversely affect the gut microbiome and cause diarrhea.

Anaesthesia and intensive care

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Development of locally relevant clinical guidelines for procedure-related neonatal analgesic practice in Kenya: a systematic review and meta-analysis
Cian Wade[1], John Scott Frazer[2], Evelyn Qian[3], Lien M Davidson[3], Suzanne Dash[2], Anna Te Water Naudé[2], Rema Ramakrishan[4], Jalemba Aluvaala[5], Kokila Lakhoo[6], Mike English[7]
Abstract
Background Increasing numbers of neonates are undergoing painful procedures in low-income and middle-income countries, with adequate analgesia seldom used. In collaboration with a multi-disciplinary team in Kenya, we aimed to establish the first evidence-based guidelines for the management of routine procedure-related neonatal pain that consider low-resource hospital settings.
Methods: We did a systematic review by searching MEDLINE, Embase, CINAHL, and CENTRAL databases for studies published from Jan 1, 1953, to March 31, 2019. We included data from randomised controlled trials using heart rate, oxygen saturation (SpO_2), premature infant pain profile (PIPP) score, neonatal infant pain scale (NIPS) score, neonatal facial coding system score, and douleur aiguë du nouveau-né scale score as pain outcome measures. We excluded studies in which neonates were undergoing circumcision or were intubated, studies from which data were unextractable, or when pain was scored by non-trained individuals. We did a narrative synthesis of all studies, and meta-analysis when data were available from multiple studies comparing the same analgesics and controls and using the same outcome measures. 17 Kenyan health-care professionals formed our clinical guideline development panel, and we used the Grading of Recommendations, Assessment, Development and Evaluation framework and the panel's knowledge of the local health-care context to guide the guideline development process. This study is registered with PROSPERO, CRD42019126620.
Findings: Of 2782 studies assessed for eligibility, data from 149 (5%) were analysed, with 80 (3%) of these further contributing to our meta-analysis. We found a high level of certainty for the superiority of breastfeeding over placebo or no intervention (standardised mean differences [SMDs] were -1·40 [95% CI -1·96 to -0·84] in PIPP score and -2·20 [-2·91 to -1·48] in

NIPS score), and the superiority of oral sugar solutions over placebo or no intervention (SMDs were -0·38 [-0·61 to -0·16] in heart rate and 0·23 [0·04 to 0·42] in SpO_2). We found a moderate level of certainty for the superiority for expressed breastmilk over placebo or no intervention (SMDs were -0·46 [95% CI -0·87 to -0·05] in heart rate and 0·48 [0·20 to 0·75] in SpO_2). Therefore, the panel recommended that breastfeeding should be given as first-line analgesic treatment, initiated at least 2 min pre-procedure. Given contextual factors, for neonates who are unable to breastfeed, 1-2 mL of expressed breastmilk should be given as first-line analgesic, or 1-2 mL of oral sugar (≥10% concentration) as second-line analgesic. The panel also recommended parental presence during procedures with adjunctive provision of skin-to-skin care, or non-nutritive sucking when possible.
Interpretation: We have generated Kenya's first neonatal analgesic guidelines for routine procedures, which have been adopted by the Kenyan Ministry of Health, and have shown a framework for clinical guideline development that is applicable to other low-income and middle-income health-care settings.

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Comparison of medication acceptance of intranasal midazolam administered by parents versus doctors in children - A randomized trial

M V S Satya Prakash[1], S Sivasankar[1], Lenin Babu Elakkumanan[1], V K Mohan[1], Rithu Krishna Kamaladevi[1]

Abstract
Background: The positive effects of midazolam as a premedication in pediatric patients are well documented. Although there are many studies regarding the route and dosage of administration, literature does not have any evidence on the outcome of medication acceptance based on the person administering the drug.
Aim: The aim of this study was to compare the medication acceptance and preoperative anxiolysis of intranasal midazolam administered by parents and anesthesiologists.
Materials and methods: This prospective randomized study was conducted in sixty children belonging to the American Society of Anesthesiologists Class 1 or 2 belonging to either sex, aged between 1 and 9 years, undergoing elective surgeries. Group P received intranasal midazolam administered by parents, whereas Group D received intranasal midazolam administered by doctors. Various scores were assessed.
Results: Children were more sedated in Group P. Clinically, medication acceptance was better in Group P when compared with Group D, but a statistically significant difference in medication acceptance was seen only in patients who are >4 years of age. Parental separation, Ramsay Sedation Score, and mask acceptance were better in Group P than in Group D.
Conclusion: Intranasal midazolam when given by parents produces better preoperative anxiolysis and easier parental separation as compared with administration by a medical staff.

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Promethazine and Oral Midazolam Preanesthetic Children Medication

Sedigheh Nadri[1], Hormoz Mahmoudvand[2], Nadereh Taee[3], Khatereh Anbari[4], Siavash Beiranvand[1]

Abstract

Aims: Several kinds of drugs have been investigated in preschool children as a preanesthetic sedation after various routes of administration for surgeries. This study aims to compare the efficacy of promethazine and oral midazolam for premedication in children aged 3 to 9 years who were scheduled for surgeries.

Methods: This is a double-blind randomized controlled study conducted on 93 patients between the age of 3 and 9 years at Loresten University of Medical Sciences Teaching Hospital, Khoramabad, Iran. The subjects were grouped into P (promethazine), M (midazolam), and C (control). About 0.3 mg/kg of oral promethazine was administered to patients in group P, 0.5 mg/kg of oral midazolam was administered to patients in group M, and 3 mL of normal saline as placebo was administered to patients in group C. Patient satisfaction, sedation and emotional score, systolic blood pressure (SBP), diastolic blood pressure, respiratory rate (RR), and heart rate (HR) were recorded.

Results: There was no statistically significant difference among the 3 groups. However, the period after medication, it was observed that SBP, diastolic blood pressure, RR, and HR in group C were statistically significantly higher than those in groups M and P. These 2 groups are similar in terms of SBP, RR, and HR. The emotional scores were comparable for the 2 groups. It was between 3.97 ± 0.6 to 1.7 ± 0.5 in group M and from 3.45 ± 1.17 to 2.745 ± 0.997 in group P in a Kruskal-Wallis test.

Conclusions: This study shows that both test groups reduce stress at the time of anesthetic induction and separation from their parents with similar effect. Both of the anesthetics are easily administered without the necessity of an additional equipment. A shorter period to maximal sedation for midazolam is an advantage, thus, making the drug helpful, mostly in the outpatient setting.

Intensive care

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Use of Honey Versus Standard Care for Hospital-Acquired Pressure Injury in Critically Ill Children: A Multicenter Randomized Controlled Trial

Jhuma Sankar[1], A V Lalitha[2], Ramachandran Rameshkumar[3], Subramanian Mahadevan[3], Sushil K Kabra[1], Rakesh Lodha[1]

Abstract

Objectives: To examine if the use of honey (medicated) for dressing is superior to standard care in terms of time to complete wound healing in stages 1-3 of pressure injuries in children admitted to the PICU.

Design: Multicenter, open-label, parallel-group, randomized trial.

Setting: Tertiary-care PICU from August 2017 to January 2019.

Patients: Critically ill children, 2 months to 17 years old, who developed pressure injury (stages 1-3) were included; those on more than two inotropes or with signs of acute wound infection or wounds with greater than 5 cm diameter or known allergy to honey were excluded.
Interventions: Children were randomized to receive either medicated honey dressing or standard (routine) wound care for the management of their pressure injury.
Measurements and main results: The primary outcome was the time to complete wound healing. Manuka or active Leptospermum honey dressing/gel was used in the intervention group. Enrolled children were followed up until death or discharge from the hospital. A total of 99 children were enrolled: 51 in the intervention group and 48 in the standard care group. Baseline characteristics, including the nutritional status, were comparable between the groups. The most common sites of injury were bony prominences at face mask contact points. The median time to complete healing was 7 days (95% CI, 6-7 d) versus 9 days (7-10 d) in the intervention and standard care groups, respectively (p = 0.002; log-rank test). At any random time, children in the intervention group were about 1.9-fold more likely to have their pressure injury completely healed than those in the standard care group (hazard ratio 1.86; 95% CI, 1.21-2.87). There were no allergic reactions or secondary wound infections in the intervention group.
Conclusions: The use of medicated honey dressings decreased the time to wound healing in critically ill children with pressure injuries. There were no allergic reactions or secondary bacterial infections in any of these children.

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Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia
Tingting Zhao[1], Xinyu Wu[1], Qi Zhang[2], Chunjie Li[3], Helen V Worthington[4], Fang Hua[1,5,6]
Abstract
Background: Ventilator-associated pneumonia (VAP) is defined as pneumonia developing in people who have received mechanical ventilation for at least 48 hours. VAP is a potentially serious complication in these patients who are already critically ill. Oral hygiene care (OHC), using either a mouthrinse, gel, swab, toothbrush, or combination, together with suction of secretions, may reduce the risk of VAP in these patients.
Objectives: To assess the effects of oral hygiene care (OHC) on incidence of ventilator-associated pneumonia in critically ill patients receiving mechanical ventilation in hospital intensive care units (ICUs).
Search methods: Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 25 February 2020), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2020, Issue 1), MEDLINE Ovid (1946 to 25 February 2020), Embase Ovid (1980 to 25 February 2020), LILACS BIREME Virtual Health Library (1982 to 25 February 2020) and CINAHL EBSCO (1937 to 25 February 2020). We also searched the VIP Database (January 2012 to 8 March 2020). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria: We included randomised controlled trials (RCTs) evaluating the effects of OHC (mouthrinse, gel, swab, toothbrush or combination) in critically ill patients receiving mechanical ventilation for at least 48 hours.
Data collection and analysis: At least two review authors independently assessed search results, extracted data and assessed risk of bias in included studies. We contacted study authors for additional information. We reported risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, using the random-effects model of meta-analysis when data from four or more trials were combined.
Main results: We included 40 RCTs (5675 participants), which were conducted in various countries including China, USA, Brazil and Iran. We categorised these RCTs into five main comparisons: chlorhexidine (CHX) mouthrinse or gel versus placebo/usual care; CHX mouthrinse versus other oral care agents; toothbrushing (± antiseptics) versus no toothbrushing (± antiseptics); powered versus manual toothbrushing; and comparisons of other oral care agents used in OHC (other oral care agents versus placebo/usual care, or head-to-head comparisons between other oral care agents). We assessed the overall risk of bias as high in 31 trials and low in two, with the rest being unclear. Moderate-certainty evidence from 13 RCTs (1206 participants, 92% adults) shows that CHX mouthrinse or gel, as part of OHC, probably reduces the incidence of VAP compared to placebo or usual care from 26% to about 18% (RR 0.67, 95% confidence intervals (CI) 0.47 to 0.97; P = 0.03; I^2 = 66%). This is equivalent to a number needed to treat for an additional beneficial outcome (NNTB) of 12 (95% CI 7 to 128), i.e. providing OHC including CHX for 12 ventilated patients in intensive care would prevent one patient developing VAP. There was no evidence of a difference between interventions for the outcomes of mortality (RR 1.03, 95% CI 0.80 to 1.33; P = 0.86, I^2 = 0%; 9 RCTs, 944 participants; moderate-certainty evidence), duration of mechanical ventilation (MD -1.10 days, 95% CI -3.20 to 1.00 days; P = 0.30, I^2 = 74%; 4 RCTs, 594 participants; very low-certainty evidence) or duration of intensive care unit (ICU) stay (MD -0.89 days, 95% CI -3.59 to 1.82 days; P = 0.52, I^2 = 69%; 5 RCTs, 627 participants; low-certainty evidence). Most studies did not mention adverse effects. One study reported adverse effects, which were mild, with similar frequency in CHX and control groups and one study reported there were no adverse effects. Toothbrushing (± antiseptics) may reduce the incidence of VAP (RR 0.61, 95% CI 0.41 to 0.91; P = 0.01, I^2 = 40%; 5 RCTs, 910 participants; low-certainty evidence) compared to OHC without toothbrushing (± antiseptics). There is also some evidence that toothbrushing may reduce the duration of ICU stay (MD -1.89 days, 95% CI -3.52 to -0.27 days; P = 0.02, I^2 = 0%; 3 RCTs, 749 participants), but this is very low certainty. Low-certainty evidence did not show a reduction in mortality (RR 0.84, 95% CI 0.67 to 1.05; P = 0.12, I^2 = 0%; 5 RCTs, 910 participants) or duration of mechanical ventilation (MD -0.43, 95% CI -1.17 to 0.30; P = 0.25, I^2 = 46%; 4 RCTs, 810 participants).
Authors' conclusions: Chlorhexidine mouthwash or gel, as part of OHC, probably reduces the incidence of developing ventilator-associated pneumonia (VAP) in critically ill patients from 26% to about 18%, when compared to placebo or usual care. We did not find a difference in mortality, duration of mechanical ventilation or duration of stay in the intensive care unit, although the evidence was low certainty. OHC including both antiseptics and toothbrushing may be more effective than OHC with antiseptics alone to reduce the incidence of VAP and the length of ICU stay, but, again, the evidence is low certainty. There is insufficient evidence to determine whether any of the interventions evaluated in the studies are associated with adverse effects.

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High-Flow Nasal Cannula Compared With Conventional Oxygen Therapy or Noninvasive Ventilation Immediately Postextubation: A Systematic Review and Meta-Analysis

David Granton[1], Dipayan Chaudhuri[1], Dominic Wang[2], Sharon Einav[3,4], Yigal Helviz[3], Tommaso Mauri[5], Jordi Mancebo[6], Jean-Pierre Frat[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20], Sameer Jog[10], Gonzalo Hernandez[11], Salvatore M Maggiore[12,13], Carol L Hodgson[14], Samir Jaber[15], Laurent Brochard[16], Vatsal Trivedi[16], Jean-Damien Ricard[17,18], Ewan C Goligher[16,19], Karen E A Burns[16,20], Bram Rochwerg[1,20]

Abstract

Objectives: Reintubation after failed extubation is associated with increased mortality and longer hospital length of stay. Noninvasive oxygenation modalities may prevent reintubation. We conducted a systematic review and meta-analysis to determine the safety and efficacy of high-flow nasal cannula after extubation in critically ill adults.

Data sources: We searched MEDLINE, EMBASE, and Web of Science.

Study selection: We included randomized controlled trials comparing high-flow nasal cannula to other noninvasive methods of oxygen delivery after extubation in critically ill adults.

Data extraction: We included the following outcomes: reintubation, postextubation respiratory failure, mortality, use of noninvasive ventilation, ICU and hospital length of stay, complications, and comfort.

Data synthesis: We included eight randomized controlled trials (n = 1,594 patients). Compared with conventional oxygen therapy, high-flow nasal cannula decreased reintubation (relative risk, 0.46; 95% CI, 0.30-0.70; moderate certainty) and postextubation respiratory failure (relative risk, 0.52; 95% CI, 0.30-0.91; very low certainty), but had no effect on mortality (relative risk, 0.93; 95% CI, 0.57-1.52; moderate certainty), or ICU length of stay (mean difference, 0.05 d fewer; 95% CI, 0.83 d fewer to 0.73 d more; high certainty). High-flow nasal cannula may decrease use of noninvasive ventilation (relative risk, 0.64; 95% CI, 0.34-1.22; moderate certainty) and hospital length of stay (mean difference, 0.98 d fewer; 95% CI, 2.16 d fewer to 0.21 d more; moderate certainty) compared with conventional oxygen therapy, however, certainty was limited by imprecision. Compared with noninvasive ventilation, high-flow nasal cannula had no effect on reintubation (relative risk, 1.16; 95% CI, 0.86-1.57; low certainty), mortality (relative risk, 1.12; 95% CI, 0.82-1.53; moderate certainty), or postextubation respiratory failure (relative risk, 0.82; 95% CI, 0.48-1.41; very low certainty). High-flow nasal cannula may reduce ICU length of stay (moderate certainty) and hospital length of stay (moderate certainty) compared with noninvasive ventilation.

Conclusions: High-flow nasal cannula reduces reintubation compared with conventional oxygen therapy, but not compared with noninvasive ventilation after extubation.

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Wall-mounted Versus Handheld Syringe Suction for Pediatric Bronchoalveolar Lavage: A Randomized Controlled Trial

Aruna D Herath[1], Kana R Jat[1], Rakesh Lodha[1], Venkateswaran K Iyer[2], Jayati Sarangi[2], Sushil K Kabra[1]

Abstract

Background: Bronchoalveolar lavage (BAL) via flexible bronchoscopy is a valuable diagnostic technique in children. The quality of BAL is directly related to the volume of the fluid recovered. Continuous wall suctioning and handheld syringe suctioning are the 2 commonly used methods, but they are rarely compared in children. We aimed to compare the above 2 suctioning techniques for BAL in the pediatric age group.

Methods: This randomized controlled study enrolled children from 1 month to 18 years of age undergoing flexible bronchoscopy and BAL. We compared continuous wall suctioning and the handheld syringe suctioning technique. The primary outcome was the percentage of BAL fluid recovery in 2 different suctioning techniques. Secondary outcomes included technical acceptable BAL and yield of various diagnostic tests in BAL.

Results: The study included 73 children (48 boys) with a median (interquartile range) age of 30 (8, 108) months. There were 37 children in the wall mount group and 36 children in the syringe suction group. Baseline characteristics of the groups were similar. The wall mount suction had more recovery of BAL fluid compared with the syringe method (43.6±8.4% vs. 37.8±8.5%, P=0.004). The proportion of BAL having a fluid recovery of ≥40% was also high in the wall mount suction [31 (83.8%) vs. 17 (47.2%); P=0.001]. There was no difference in diagnostic yield between the groups.

Conclusion: Wall mount suction had better BAL fluid recovery compared with handheld syringe suction in children undergoing flexible bronchoscopy. The diagnostic yield was similar in both groups.

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Randomized Clinical Trial of 20% Mannitol Versus 3% Hypertonic Saline in Children With Raised Intracranial Pressure Due to Acute CNS Infections

Ramachandran Rameshkumar[1], Arun Bansal, Sunit Singhi, Pratibha Singhi, Muralidharan Jayashree

Abstract

Objectives: Mannitol is a commonly used osmotherapy agent in raised intracranial pressure. However, the side effects of mannitol are significant. In traumatic brain injury (adult and pediatric), hypertonic saline (3%) shows varied results in comparison with 20% mannitol. We compared the effect of 3% hypertonic saline versus 20% mannitol (using common dosing strategies) on raised intracranial pressure in pediatric acute CNS infections.

Design: Open-label randomized controlled trial.

Setting: PICU of a quaternary care academic institute.

Patients: Children 1-12 years old, with raised intracranial pressure and modified-Glasgow Coma Scale scores less than or equal to 8, were enrolled.

Interventions: Patients were randomly assigned to 20%-mannitol (n = 28), 0.5 gram/kg/dose versus 3%-hypertonic saline (n = 29), 10 mL/kg loading followed by 0.5-1 mL/kg/hr infusion. An intraparenchymal catheter was used to monitor the intracranial pressure. The primary outcome was the proportion of patients achieved target average intracranial pressure less

than 20 mm Hg during 72 hours. Secondary outcomes were interventions, morbidity, and mortality.
Measurements and main results: The proportion of patients with target average intracranial pressure (< 20 mm Hg) was higher in hypertonic saline-group as compared to mannitol-group (79.3% vs 53.6%; adjusted hazard ratio 2.63; 95% CI: 1.23-5.61). Mean (± SE) reduction of intracranial pressure (-14.3 ± 1.7 vs -5.4 ± 1.7 mm Hg; p ≤ 0.001) and elevation of cerebral perfusion pressure (15.4 ± 2.4 vs 6 ± 2.4 mm Hg; p = 0.007) from baseline were significant in hypertonic saline-group. Mean (± SE) intracranial pressure over 72 hours was lower (14 ± 2 vs 22 ± 2 mm Hg; p = 0.009), and cerebral perfusion pressure was higher (65 ± 2.2 vs 58 ± 2.2; p = 0.032) in hypertonic saline-group. Hypertonic saline-group had higher modified-Glasgow Coma Scale score at 72 hours (median, interquartile range 10; 7-11 vs 7; 3-9; p = 0.003), lower mortality (20.7% vs 35.7%; p = 0.21), shorter duration of mechanical ventilation (5 vs 15 d; p = 0.002), and PICU stay (11 vs 19 d; p = 0.016) and less severe neurodisability at discharge (31% vs 61%; p = 0.049).
Conclusions: In pediatric acute CNS infections, 3%-hypertonic saline was associated with a greater reduction of intracranial pressure as compared to 20% mannitol.

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Trial of Furosemide to Prevent Acute Kidney Injury in Critically Ill Children: A Double-Blind, Randomized, Controlled Trial
Shilpa Abraham[1], Ramachandran Rameshkumar[2], Muthu Chidambaram[1], Rajendran Soundravally[3], Seenivasan Subramani[1], Rohit Bhowmick[1], Abraar Sheriff[1], Kaushik Maulik[1], Subramanian Mahadevan[1]
Abstract
Objective: To study whether furosemide infusion in early-onset acute kidney injury (AKI) in critically ill children would be associated with a reduced proportion of patients progressing to the higher stage (Injury or Failure) as compared to placebo.
Method: A double-blind, placebo-controlled, randomized pilot trial was conducted. The authors enrolled children aged 1-mo (corrected) to 12-y, who were diagnosed with AKI ("risk" stage) using pediatric-Risk, Injury, Failure, Loss, End stage kidney disease (p-RIFLE) criteria, and achieved immediate resuscitation goals within 24 h of admission. Participants received either furosemide (0.05 to 0.4 mg/kg/h) or placebo (5%-dextrose) infusion. The primary outcome was the proportion of patients progressing to a higher stage (injury or failure). Secondary outcomes were (i) need for renal replacement therapy, (ii) the effect on neutrophil gelatinase-associated lipocalin (urine and blood), (iii) fluid balance, (iv) adverse effects, (v) time to achieve renal recovery, (vi) duration of hospital stay and mechanical ventilation, and (vii) all-cause 28-d mortality.
Results: The trial was stopped for futility, and data were analyzed on an intention-to-treat basis (furosemide-group: n = 38; placebo-group: n = 37). No significant difference was noted in the progression of AKI to a higher stage between furosemide and placebo groups (10.5% vs. 21.6%; relative risk = 0.49, 95% CI 0.16 to 1.48) (p = 0.22). There were no differences in the secondary outcomes between the study groups. All-cause 28-d mortality was similar between the groups (10.5% vs. 10.8%). No trial-related severe adverse events occurred.

Conclusions: Furosemide infusion in early-onset AKI did not reduce the progression to a higher stage of AKI. A future trial with large sample size is warranted.
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Dexmedetomidine vs Midazolam for Sedation in Mechanically Ventilated Children: A Randomized Controlled Trial

Krishna Mohan Gulla[1], Jhuma Sankar[1], Kana Ram Jat[1], Sushil Kumar Kabra[1], Rakesh Lodha[2]

Abstract

Background: There is a paucity of data on use of dexmedetomidine as a sedative agent in mechanically ventilated children.

Objectives: To compare the efficacy of dexmedetomidine and midazolam for sedation in mechanically ventilated children aged 1 month - 15 years. Secondary objectives were to compare the need for top-up doses of fentanyl and paralytic agents, duration of mechanical ventilation, ICU stay and hospital stay, and adverse events.

Design: Open label, non-inferiority, randomized controlled trial.

Setting: PICU of a tertiary care teaching hospital in India.

Patients: Consecutive children aged 1 month to 15 years who were mechanically ventilated.

Intervention: Children were randomized to either dexmedeto-midine or midazolam and the doses were titrated to maintain target sedation score of 4 or 5 as measured by Penn State Children Hospital Sedation algorithm.

Outcome: The percentage of time spent in level 4 or 5 of Penn State Children Hospital sedation algorithm for ventilated children.

Results: 49 children were randomized (24 to 'midazolam group' and 25 to 'dexmedetomidine group'). There was no difference in the percentage of time spent in the targeted sedation between the groups [midazolam 67.3% (18.8) vs. dexmedetomidine 56.3 %. (28.6); P=0.12]. The absolute difference in the percentage of time spent was -10.9% [SE (95% CI) 7.05: (-25.15 to 3.25)]. The lower end of 95% CI for the difference breached the non-inferiority limit of -20%. Number of fentanyl boluses, duration of mechanical ventilation, ICU stay, and hospital stay were similar. Four (17.4%) children in dexmedetomidine group developed persistent bradycardia.

Conclusion: Non-inferiority of dexmedetomidine compared to midazolam for sedation in children on mechanical ventilation could not be established.

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Efficacy of chlorhexidine patches on central line-associated bloodstream infections in children

Nattapong Jitrungruengnij[1 2], Suvaporn Anugulruengkitt[1 2], Thanapoom Rattananupong[3], Mayuree Prinyawat[4], Watsamon Jantarabenjakul[1 2 5], Noppadol Wacharachaisurapol[1 2], Tanittha Chatsuwan[6], Pakpoom Janewongwirot[1 2], Pintip Suchartlikitwong[1 2], Monta Tawan[2], Phavinee Kanchanabutr[7], Chitsanu Pancharoen[1 2], Thanyawee Puthanakit[1 2]

Abstract

Background: Central line-associated bloodstream infections (CLABSIs) are important hospital-acquired infections. Chlorhexidine-impregnated dressings (also known as chlorhexidine patches, CHG patches) are reported to decrease CLABSIs in adults. This study aims to determine the efficacy of CHG patches in reducing CLABSIs in children.
Methods: An open-label randomized controlled trial was conducted in children aged 2 months to 18 years, requiring a short-term catheter. Patients were randomized into two groups, allocated to receive CHG patches or standard transparent dressings. Care of the catheter was in accordance with Asia Pacific Society of Infection Control (APSIC) recommendations. Central-line-associated bloodstream infections were defined using National Healthcare Safety Network surveillance criteria.
Results: From April 2017 to April 2018, 192 children were enrolled. There were 108 CHG patch catheters and 101 standard dressing catheters, contributing to 3,113 catheter days. The median duration of catheter dwelling was 13 days, with an interquartile range (IQR) of 8-20 days. Half were placed at the jugular vein and 22% at the femoral vein. There were 23 CLABSI events. Incidence rates for CHG patches and standard dressings were 7.98 (95% confidence interval (CI), 4.25-13.65) and 6.74 (95% CI, 3.23-12.39) per 1,000 catheter days, respectively (incidence rate ratio 1.18; 95% CI, 0.52-2.70). The CLABSI pathogens were 15 Gram-negative bacteria, six Gram-positive bacteria, and two Candida organisms. Catheter colonization of CHG patches and standard dressings were 2.02 (95% CI, 0.42-5.91) and 3.07 (95% CI, 1.00-7.16) per 1,000 catheter days, respectively. Only local adverse effects occurred in 6.8% of the participants.
Conclusions: In our setting, there was no difference in CLABSI rates when the chlorhexidine patch dressings were compared with the standard transparent dressings. Strengthening of CLABSI prevention bundles is mandatory.

Antibiotics

Azithromycin mass drug administration

(see also Ophthalmology - Trachoma)

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Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution

Thuy Doan[1], Lee Worden[1], Armin Hinterwirth[1], Ahmed M Arzika[1], Ramatou Maliki[1], Amza Abdou[1], Lina Zhong[1], Cindi Chen[1], Catherine Cook[1], Elodie Lebas[1], Kieran S O'Brien[1], Catherine E Oldenburg[1], Eric D Chow[1], Travis C Porco[1], Marc Lipsitch[1], Jeremy D Keenan[1], Thomas M Lietman[1]

Abstract
Background: Mass distribution of azithromycin to preschool children twice yearly for 2 years has been shown to reduce childhood mortality in sub-Saharan Africa but at the cost of amplifying macrolide resistance. The effects on the gut resistome, a reservoir of

antimicrobial resistance genes in the body, of twice-yearly administration of azithromycin for a longer period are unclear.
Methods: We investigated the gut resistome of children after they received twice-yearly distributions of azithromycin for 4 years. In the Niger site of the MORDOR trial, we enrolled 30 villages in a concurrent trial in which they were randomly assigned to receive mass distribution of either azithromycin or placebo, offered to all children 1 to 59 months of age every 6 months for 4 years. Rectal swabs were collected at baseline, 36 months, and 48 months for analysis of the participants' gut resistome. The primary outcome was the ratio of macrolide-resistance determinants in the azithromycin group to those in the placebo group at 48 months.
Results: Over the entire 48-month period, the mean (±SD) coverage was 86.6±12% in the villages that received placebo and 83.2±16.4% in the villages that received azithromycin. A total of 3232 samples were collected during the entire trial period; of the samples obtained at the 48-month monitoring visit, 546 samples from 15 villages that received placebo and 504 from 14 villages that received azithromycin were analyzed. Determinants of macrolide resistance were higher in the azithromycin group than in the placebo group: 7.4 times as high (95% confidence interval [CI], 4.0 to 16.7) at 36 months and 7.5 times as high (95% CI, 3.8 to 23.1) at 48 months. Continued mass azithromycin distributions also selected for determinants of nonmacrolide resistance, including resistance to beta-lactam antibiotics, an antibiotic class prescribed frequently in this region of Africa.
Conclusions: Among villages assigned to receive mass distributions of azithromycin or placebo twice yearly for 4 years, antibiotic resistance was more common in the villages that received azithromycin than in those that received placebo. This trial showed that mass azithromycin distributions may propagate antibiotic resistance.

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Biannual azithromycin distribution and child mortality among malnourished children: A subgroup analysis of the MORDOR cluster-randomized trial in Niger
Kieran S O'Brien[1,2], Ahmed M Arzika[3], Ramatou Maliki[3], Farouk Manzo[3], Alio K Mamkara[3], Elodie Lebas[1], Catherine Cook[1], Robin L Bailey[4], Sheila K West[5], Catherine E Oldenburg[1], Travis C Porco[1,6,7,8], Benjamin Arnold[1,6], Jeremy D Keenan[1,6], Thomas M Lietman[1,6,7,8], MORDOR Study Group
Abstract
Background: Biannual azithromycin distribution has been shown to reduce child mortality as well as increase antimicrobial resistance. Targeting distributions to vulnerable subgroups such as malnourished children is one approach to reaching those at the highest risk of mortality while limiting selection for resistance. The objective of this analysis was to assess whether the effect of azithromycin on mortality differs by nutritional status.
Methods and findings: A large simple trial randomized communities in Niger to receive biannual distributions of azithromycin or placebo to children 1-59 months old over a 2-year timeframe. In exploratory subgroup analyses, the effect of azithromycin distribution on child mortality was assessed for underweight subgroups using weight-for-age Z-score (WAZ) thresholds of -2 and -3. Modification of the effect of azithromycin on mortality by underweight status was examined on the additive and multiplicative scale. Between

December 2014 and August 2017, 27,222 children 1-11 months of age from 593 communities had weight measured at their first study visit. Overall, the average age among included children was 4.7 months (interquartile range [IQR] 3-6), 49.5% were female, 23% had a WAZ < -2, and 10% had a WAZ < -3. This analysis included 523 deaths in communities assigned to azithromycin and 661 deaths in communities assigned to placebo. The mortality rate was lower in communities assigned to azithromycin than placebo overall, with larger reductions among children with lower WAZ: -12.6 deaths per 1,000 person-years (95% CI -18.5 to -6.9, P < 0.001) overall, -17.0 (95% CI -28.0 to -7.0, P = 0.001) among children with WAZ < -2, and -25.6 (95% CI -42.6 to -9.6, P = 0.003) among children with WAZ < -3. No statistically significant evidence of effect modification was demonstrated by WAZ subgroup on either the additive or multiplicative scale (WAZ < -2, additive: 95% CI -6.4 to 16.8, P = 0.34; WAZ < -2, multiplicative: 95% CI 0.8 to 1.4, P = 0.50, WAZ < -3, additive: 95% CI -2.2 to 31.1, P = 0.14; WAZ < -3, multiplicative: 95% CI 0.9 to 1.7, P = 0.26). The estimated number of deaths averted with azithromycin was 388 (95% CI 214 to 574) overall, 116 (95% CI 48 to 192) among children with WAZ < -2, and 76 (95% CI 27 to 127) among children with WAZ < -3. Limitations include the availability of a single weight measurement on only the youngest children and the lack of power to detect small effect sizes with this rare outcome. Despite the trial's large size, formal tests for effect modification did not reach statistical significance at the 95% confidence level. **Conclusions:** Although mortality rates were higher in the underweight subgroups, this study was unable to demonstrate that nutritional status modified the effect of biannual azithromycin distribution on mortality. Even if the effect were greater among underweight children, a nontargeted intervention would result in the greatest absolute number of deaths averted.

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doi: 10.4269/ajtmh.19-0500.

Impact of Biannual Azithromycin on Anemia in Preschool Children in Kilosa District, Tanzania: A Cluster-Randomized Clinical Trial

Evan M Bloch[1], Beatriz Munoz[2], Jerusha Weaver[2], Zakayo Mrango[3], Thomas M Lietman[4], Sheila K West[2]

Abstract

A cluster-randomized clinical trial showed that biannual single-dose azithromycin reduced mortality in preschool children; we sought to determine the effect on anemia. A simple random sample of 30 communities from Kilosa district, Tanzania, were themselves randomized to receive either 6-monthly treatment of children aged 1-59 months with single-dose azithromycin or placebo. From each community, 40 preschool children were randomly selected at baseline, 12 months, and 24 months. At surveys, the children underwent hemoglobin testing; WHO definitions for anemia were applied. After adjusting for community clustering, the prevalence of anemia was not significantly different by treatment assignment at baseline, 12 months, and 24 months. In each of the cross-sectional surveys, anemia prevalence was associated with younger age; the odds of being anemic was highest in those aged < 12 months. There was also a general decrease in the prevalence of anemia during the study. Although azithromycin was not shown to affect anemia, significantly, the study highlights burden of anemia in rural, African communities.

Am J Trop Med Hyg. 2020 Sep;103(3):1315-1318.
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Malaria Parasitemia and Nutritional Status during the Low Transmission Season in the Presence of Azithromycin Distribution among Preschool Children in Niger

Ahmed M Arzika[1], Ramatou Maliki[1], Nameywa Boubacar[1], Salissou Kane[1], Catherine A Cook[2], Elodie Lebas[2], Ying Lin[2], Kieran S O'Brien[2], Ariana Austin[2], Jeremy D Keenan[3,2], Thomas M Lietman[4,3,2], Catherine E Oldenburg[2,4,3], For The Mordor Study Group

Abstract

The relationship between malaria and malnutrition is complicated, and existence of one may predispose or exacerbate the other. We evaluated the relationship between malaria parasitemia and nutritional status in children living in communities participating in a cluster-randomized trial of biannual azithromycin compared with placebo for prevention of childhood mortality. Data were collected during the low malaria transmission and low food insecurity season. Parasitemia was not associated with weight-for-height *Z*-score (24 months: $P = 0.11$ azithromycin communities, $P = 0.75$ placebo communities), weight-for-age *Z*-score (24 months: $P = 0.83$ azithromycin, $P = 0.78$ placebo), height-for-age *Z*-score (24 months: $P = 0.30$ azithromycin, $P = 0.87$ placebo), or mid-upper arm circumference (24 months: $P = 0.12$ azithromycin, $P = 0.56$ placebo). There was no statistically significant evidence of a difference in the relationship in communities receiving azithromycin or placebo. During the low transmission season, there was no evidence that malaria parasitemia and impaired nutritional status co-occur in children.

Am J Trop Med Hyg. 2020 Sep;103(3):1283-1290.
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Cost-Effectiveness of Mass Treatment with Azithromycin for Reducing Child Mortality in Malawi: Secondary Analysis from the MORDOR Trial

John D Hart[1], Khumbo Kalua[2], Jeremy D Keenan[3], Thomas M Lietman[3], Robin L Bailey[1]

Abstract

The recent Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) trial reported a reduction in child mortality following biannual azithromycin mass drug administration (MDA). Here, we investigate the financial costs and cost-effectiveness from the health provider perspective of azithromycin MDA at the MORDOR-Malawi study site. During MORDOR, a cluster-randomized trial involving biannual azithromycin MDA or placebo to children aged 1-59 months, fieldwork-related costs were collected, including personnel, transport, consumables, overheads, training, and supervision. Mortality rates in azithromycin- and placebo-treated clusters were calculated overall and for the five health zones of Mangochi district. These were used to estimate the number needed to treat to avert one death and the costs per death and disability-adjusted life year (DALY) averted. The cost per dose of MDA was $0.74 overall, varying between $0.63 and $0.94 in the five zones. Overall, the number needed to treat to avert one death was 1,213 children; the cost per death averted was $898.47, and the cost per DALY averted was $9.98. In the three zones where mortality

was lower in azithromycin-treated clusters, the number needed to treat to avert one death, cost per death averted, and cost per DALY averted, respectively, were as follows: 3,070, $2,899.24, and $32.31 in Monkey Bay zone; 1,530, $1,214.42, and $13.49 in Chilipa zone; and 344, $217.98, and $2.42 in Namwera zone. This study is a preliminary cost-effectiveness analysis that indicates azithromycin MDA for reducing child mortality has the potential to be highly cost-effective in some settings in Malawi, but the reasons for geographical variation in effectiveness require further investigation.

Clin Infect Dis. 2020 Nov 19;71(16):2282-2284.
doi: 10.1093/cid/ciaa606.

Reduction of Coronavirus Burden With Mass Azithromycin Distribution

Thuy Doan[1,2], Armin Hinterwirth[1,2], Ahmed M Arzika[3], Lee Worden[1], Cindi Chen[1], Lina Zhong[1], Catherine E Oldenburg[1,2], Jeremy D Keenan[1,2], Thomas M Lietman[1,2]

Abstract

We evaluated the potential antiviral effects of azithromycin on the nasopharyngeal virome of Nigerien children who had received multiple rounds of mass drug administration. We found that the respiratory burden of non-severe acute respiratory syndrome coronaviruses was decreased with azithromycin distributions.

Am J Trop Med Hyg. 2020 Oct;103(4):1397-1404.
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Baseline Characteristics of Study Participants in the Early Life Interventions for Childhood Growth and Development in Tanzania (ELICIT) Trial

Tarina C Parpia[1], Sarah E Elwood[1], Rebecca J Scharf[2], Joann M McDermid[1], Anne W Wanjuhi[2], Elizabeth T Rogawski McQuade[1], Jean Gratz[1], Erling Svensen[3], Jonathan R Swann[4], Jeffrey R Donowitz[5], Samwel Jatosh[6], Siphael Katengu[6], Paschal Mdoe[6], Sokoine Kivuyo[7], Eric R Houpt[1], Mark D DeBoer[2], Estomih Mduma[6], James A Platts-Mills[1]

Abstract

Recurrent enteric infections and micronutrient deficiencies, including deficiencies in the tryptophan-kynurenine-niacin pathway, have been associated with environmental enteric dysfunction, potentially contributing to poor child growth and development. We are conducting a randomized, placebo-controlled, 2 × 2 factorial interventional trial in a rural population in Haydom, Tanzania, to determine the effect of 1) antimicrobials (azithromycin and nitazoxanide) and/or 2) nicotinamide, a niacin vitamer, on attained length at 18 months. Mother/infant dyads were enrolled within 14 days of the infant's birth from September 2017 to September 2018, with the follow-up to be completed in February 2020. Here, we describe the baseline characteristics of the study cohort, risk factors for low enrollment weight, and neonatal adverse events (AEs). Risk factors for a low enrollment weight included being a firstborn child (-0.54 difference in weight-for-age *z*-score [WAZ] versus other children, 95% CI: -0.71, -0.37), lower socioeconomic status (-0.28, 95% CI: -0.43, -0.12 difference in WAZ), and birth during the preharvest season (November to March) (-0.22, 95% CI: -0.33, -0.11 difference in WAZ). The most common neonatal serious AEs were respiratory tract infections and

neonatal sepsis (2.2 and 1.4 events per 100 child-months, respectively). The study cohort represents a high-risk population for whom interventions to improve child growth and development are urgently needed. Further analyses are needed to understand the persistent impacts of seasonal malnutrition and the interactions between seasonality, socioeconomic status, and the study interventions.

Antibiotic resistance and stewardship

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A systematic review of antimicrobial susceptibility testing as a tool in clinical trials assessing antimicrobials against infections due to Gram negative pathogens. Intended category: systematic review

Andrew Henderson[1], Evan Bursle[2], Adam Stewart[3], Patrick Na Harris[4], David Paterson[5], Mark D Chatfield[5], Mical Paul[6], Yaakov Dickstein[6], Jesus Rodriguez-Baño[7], John D Turnidge[8], Gunnar Kahlmeter[9]

Abstract

Background: Antimicrobial susceptibility testing (AST) is the standard of care for treating bacterial infections. In randomized clinical trials of new antimicrobials, AST might not be performed or reported in real time.

Objectives: To determine local, real-time laboratory AST performance, its usage in the trial flow, quality control (QC) of the local testing, central AST performance and the effect of using AST categorisation on the trials' primary outcomes.

Data sources: We systematically searched PubMed, Embase, PsychINFO and Web of Science.

Eligibility criteria: We included registered randomized-controlled trials published in journals between January 2015 and December 2019.

Participants: and interventions: We included trials comparing between different antibiotics for the treatment of infections caused predominantly by Gram-negative bacteria.

Methods: Primary outcomes for different trial populations were extracted and differences between trial arms were compared for patients with infections caused by susceptible vs. non-susceptible bacteria. Results are described narratively.

Results: Of 32 randomized trials, 25 trials reported that local AST was performed, 1312 reported the local laboratory AST methods, no trial reported QC, but post-hoc referral for AST at a reference laboratory was common. Patients' outcomes were superior when patients with infections due to susceptible and non-susceptible pathogens were compared post-hoc (median difference 14%, IQR 8 to 24%) in trials allowing this comparison (7 antimicrobials), except for colistin, where 14-day mortality was 9% higher when patients were treated with colistin for colistin-susceptible vs. colistin-resistant carbapenem-resistant A. baumannii. When excluding patients with pathogens non-susceptible to either antimicrobial in the trials, the difference in the primary outcome between the trial arms was reduced in 5 out of 6 trials.

Conclusions: Trials should perform AST to guide patient inclusion or exclusion from the study and consider the impact of the central laboratory susceptibility results on the study outcomes when using post-hoc reference testing.

J Trop Pediatr. 2020 Nov 22;fmaa093.
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Antimicrobial Prescribing during Infant Hospital Admissions in a Birth Cohort in Dhaka, Bangladesh

Katherine Boone[1,2], Shaun K Morris[1,2,3], Sejal Doshi[2], Jason Black[2], Minhazul Mohsin[4], Tahmeed Ahmed[4], Abdullah Al Mahmud[4], Daniel E Roth[1,2]

Abstract

Empirical antimicrobial use is common in hospitalized infants and may contribute to antimicrobial resistance in low- and middle-income countries. In this observational birth cohort study nested in a randomized controlled trial in Dhaka, Bangladesh, inpatient antimicrobial prescription data were extracted from serious adverse event forms completed for hospitalizations of infants (0-12 months of age). The primary outcome was the proportion of inpatient admissions where systemic antimicrobials were prescribed. Infant and hospitalization-related factors associated with antimicrobial prescriptions were determined. Among 1254 infants, there were 448 admissions to 32 facilities from 2014 to 2016. Antimicrobials were prescribed in 73% of admissions with a mean antimicrobial exposure rate of 0.25 antimicrobials per day of admission [95% confidence intervals (95% CIs): 0.24-0.27]. The most common antibiotics were aminoglycosides (29%), penicillins (26%) and third-generation cephalosporins (25%). In all, 58% of antibiotics were classified as 'access', 38% 'watch' and 1% 'reserve' using the World Health Organization (WHO) Essential Medicines List classification. WHO-recommended antimicrobial regimens were used in 68% of neonatal sepsis and 9% of lower respiratory tract infection (LRTI) admissions. 'Watch' antimicrobials were used in 26% of neonatal sepsis and 76% of LRTI admissions. Compared with private facilities, antimicrobial prescription rates were lower at government [rate ratio (RR) 0.71; 95% CI: 0.61-0.83] and charitable facilities (RR 0.39; 95% CI: 0.28-0.53), after adjustment for household wealth index and parental education. Younger infant age, older maternal age and longer admission were associated with higher prescription rates. These findings highlight the need for paediatric antimicrobial stewardship programs in Bangladesh.

Asthma

Thorax. 2021 Jan 21;76(5):434-440.
doi: 10.1136/thoraxjnl-2020-216065. Online ahead of print.

An enhanced care package to improve asthma management in Malawian children: a randomised controlled trial

Sarah Rylance[1,2], Beatrice Chinoko[2], Bright Mnesa[2], Chris Jewell[3], Jonathan Grigg[4], Kevin Mortimer[5,6]

Abstract

Background: Shortages of clinical staff make chronic asthma care challenging in low-income countries. We evaluated an outpatient asthma care package for children, including task-shifting of asthma management roles.

Methods: We conducted a non-blinded individually randomised controlled trial at a tertiary-level government hospital in Blantyre, Malawi. Children aged 6-15 years diagnosed with asthma were recruited from outpatient clinic, stratified by Childhood Asthma Control Test (cACT) score and allocated 1:1 from a concealed file, accessed during electronic questionnaire completion. The intervention, delivered by non-physicians, comprised clinical assessment, optimisation of inhaled treatment, individualised asthma education. The control group received standard care from outpatient physicians. Primary outcome for intention-to-treat analysis was change in cACT score at 3 months. Secondary outcomes included asthma exacerbations requiring emergency healthcare and school absence.
Findings: Between September 2018 and December 2019, 120 children (59 intervention; 61 control) were recruited; 65.8% males, with mean (SD) age 9.8 (2.8) years, mean (SD) baseline cACT 20.3 (2.6). At 3 months, intervention children (n=56) had a greater mean (SD) change in cACT score from baseline (2.7 (2.8) vs 0.6 (2.8)) compared with standard care participants (n=59); a difference of 2.1 points (95% CI: 1.1 to 3.1, p<0.001). Fewer intervention children attended emergency healthcare (7.3% vs 25.4%, p=0.02) and missed school (20.0% vs 62.7%, p<0.001) compared with standard care children.
Interpretation: The intervention resulted in decreased asthma symptoms and exacerbations. Wider scale-up could present substantial benefits for asthmatic patients in resource-limited settings.

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doi: 10.1007/s12098-021-03753-1. Online ahead of print.

Once-Daily vs. Twice-Daily Administration of Inhaled Budesonide for Mild and Moderate Well-Controlled Childhood Asthma: A Randomized, Controlled Trial

Megha Goyal[1], Vishal Guglani[1], Pankaj Kumar[2], Shivani Randev[1]

Abstract
Objectives: To compare median change in morning peak expiratory flow rate (PEFR) and clinical asthma control in children receiving total daily dosage of inhaled budesonide administered either as once-daily or divided twice-daily dose.
Methods: It was a randomized, parallel group, open label, noninferiority trial on 80 children aged 5-12 y with mild or moderate well-controlled asthma. Baseline parameters were recorded and subjects received inhaled budesonide either as once-daily or divided twice-daily dose. Primary outcome was median change in morning PEFR. Secondary outcomes included median change in evening and diurnal variation in PEFR, asthma symptom control as per Global Initiative for Asthma, 2017 and Asthma Control Questionnaire, and spirometric measurements taken at the clinic.
Results: The median [interquartile range (IQR)] increase in morning PEFR was more in children receiving once-daily as compared to those receiving twice-daily inhaled budesonide (by 6:00 L/min; IQR: -44.00-63.00 L/min vs. 4:00 L/min; IQR: -67.50-67.50 L/min, p 0.222; 95% CI: -1.37 to 19.08). Other spirometric variables and symptoms scores were also nonsignificant except median change in evening PEFR which was in favor of twice-daily regimen.
Conclusion: Once-daily administration of inhaled budesonide is noninferior to twice-daily administration of equivalent daily dosage of inhaled budesonide.

Pediatr Pulmonol. 2021 Jun;56(6):1427-1433.
doi: 10.1002/ppul.25287. Epub 2021 Feb 1.

Vitamin-D supplementation as an adjunct to standard treatment of asthma in children: A randomized controlled trial (ViDASTA Trial)

Chirag Thakur[1], Jogender Kumar[2], Prawin Kumar[1], Jagdish Prasad Goyal[1], Kuldeep Singh[1], Atul Gupta[3]

Abstract

Objective: To determine the role of vitamin D supplementation as an adjunct to standard treatment in childhood asthma.

Study design: In this placebo-controlled, blinded, randomized controlled trial, we enrolled 60 children aged 6 to 11 years with moderate persistent asthma and randomly assigned them into intervention (2000 IU per day of vitamin D) and placebo groups (n = 30 each). The primary outcome was asthma control as assessed by the childhood asthma control test (C-ACT) scores at 12 weeks post-randomization. The secondary outcomes were improvement in the forced expiration in 1 s (FEV_1), fractional exhaled nitric oxide (FeNO), asthma exacerbations, use of systemic steroids, number of emergency visits, post-intervention vitamin D levels, and adverse outcomes. We analyzed by intention to treat.

Results: There was no significant difference between the C-ACT score in the two groups (median [first-third quartile] scores were 25 [24-26] in both groups, p = 0.7). Also, there was no significant difference between the two groups in terms of the FEV_1, FeNO, number of exacerbations, emergency visits, hospital admissions, and adverse outcomes. However, the post-intervention vitamin D levels (ng/ml) were significantly higher in the intervention group (35.5 vs. 18.8; p < 0.001). As compared to the baseline, both the groups showed better asthma control at 12 weeks post-intervention, irrespective of the type of intervention.

Conclusion: Vitamin-D supplementation as an adjunct to standard treatment does not improve asthma control in children.

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doi: 10.1007/s12098-021-03675-y. Online ahead of print.

Yoga Therapy as an Adjuvant in Management of Asthma

Pallavi Yadav[1], Pankaj Kumar Jain[1], B S Sharma[2], Meenakshi Sharma[3]

Abstract

Objective: To assess the effect of yoga on control of asthma in children with bronchial asthma.

Methods: This hospital-based interventional randomized controlled trial conducted in the Department of Pediatrics at a tertiary care center of North India from November 2017 to October 2018 enrolled 140 newly diagnosed cases of asthma of age 10-16 y who were randomly divided into two groups. Seventy children in the case group practiced yoga under supervision for a period of 3 mo in addition to pharmacological treatment. Seventy controls received only pharmacological treatment. Pulmonary-function tests were done at baseline, 6 wk, and 12 wk along with quality of life (QOL) assessment by Pediatric Asthma Quality of Life Questionnaire (PAQLQ). The outcome measures assessed were forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC and peak expiratory flow rate

(PEFR). QOL evaluation was done in 3 domains: activity limitation, symptoms, and emotional function.
Results: The asthmatic children practicing yoga have shown significant improvement in FVC, FEV1, FEV1/FVC and PEFR which was better as compared to controls. Improvement was also noted in mean-PAQLQ score in cases which was statistically significantly better as compared to controls.
Conclusion: Yoga appears to have significant positive effect on control of asthma measured by pulmonary-function test and QOL. Therefore yoga therapy can be recommended as an adjuvant in management of asthma along with standard pharmacological management.

Complimentary or traditional medicine

Complement Ther Clin Pract. 2021 Feb;42:101297.
doi: 10.1016/j.ctcp.2020.101297. Epub 2020 Dec 16.
Efficacy and safety of yinqiao powder combined with western medicine in the treatment of pneumonia: A systematic review and meta-analysis
Yihua Fan[1], Wei Liu[2], Renhong Wan[3], Shaopeng Du[4], Aihua Wang[4], Qing Xie[4], Rumeng Yang[4]
Abstract
Objective: This review aimed at systematically evaluating the efficacy and safety of Yinqiao powder combined with western medicine in the treatment of pneumonia.
Methods: A systematic search for randomized controlled trials (RCTs) focusing on pneumonia treatment using a combination of Yinqiao powder and western medicine was performed in PubMed, the Cochrane Library, EMBASE, Web of Science, CNKI, Wanfang, Weipu (VIP) and CBM. The retrieval time limit was from the establishment of the database to June 2020. Two researchers independently screened the literature, extracted the data and evaluated the bias risk of the included studies. A meta-analysis was performed using RevMan5.3 software. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
Result: Fifteen RCTs involving 1705 patients were included in the analysis. The meta-analysis results revealed the total effective rate of the treatment group [RR = 1.21, 95% CI (1.15, 1.27), P < 0.00001], bacterial clearance rate [RR = 1.13, 95% CI (1.05, 1.22), P = 0.001], adverse reactions [RR = 0.54, 95% CI (0.38, 0.76), P = 0.0005]. There were statistically significant differences in the cooling time, T cell number, procalcitonin (PCT) and C-reactive protein (CRP) value decline rate (P < 0.05). There was no statistically significant difference in the decline rate of neutrophils and leukocytes (P > 0.05).
Conclusion: The current evidence indicated that the Yinqiao powder combined with western medicine can improve total efficiency in the treatment of pneumonia patients. The combination therapy performed better when compared to western medicine alone in the cooling time, bacterial clearance rate, T cell count, decline rates of CRP and PCT as well as in the incidences of adverse reactions. However, there was no significant difference in the decline rates of neutrophils and leucocytes between the two groups. The funnel plot, Egger's test and Begg's test indicated publication bias, which may be associated with unpublished negative study results. Due to the limitation of the quality and quantity of the included studies, more high-quality studies should be performed to verify our conclusions.

Complement Ther Med. 2021 Jan;56:102606.
doi: 10.1016/j.ctim.2020.102606. Epub 2020 Nov 13.

Effect of Mind Sound Resonance Technique (MSRT - A yoga-based relaxation technique) on psychological variables and cognition in school children: A randomized controlled trial

U S Anusuya[1], Sriloy Mohanty[2], Apar Avinash Saoji[3]

Abstract

Objective: School children undergo stress, which could impact their psychological functions and cognitive abilities. Yoga practices have been found useful in enhancing psychological functions and performance. The current study was planned to evaluate a yoga-based relaxation technique's efficacy as an extracurricular activity on psychological state and cognitive function.

Design and setting: This study was a parallel-group randomized controlled trial conducted at a government school in south India.

Participants: Sixty students with age ranging between 14-16 years (mean age ± SD; 15.3 ± 0.71 years) satisfying the inclusion and exclusion criteria were randomized to experimental and control groups with an allocation ratio of 1:1.

Intervention: Experimental group received Mind Sound Resonance Technique (MSRT), whereas the control group performed supine rest (SR) for two-weeks.

Outcome measures: Participants were assessed with State trait anxiety inventory - short form, Mind Wandering Questionnaire, State Mindfulness Attention Awareness Scale, and Trail making task at baseline and post-intervention.

Results: Experimental group showed a reduction in state anxiety and mind wandering with improvement in state mindfulness and performance in the Trail-making task compared to the control group.

Conclusion: Results of the current trial indicate the beneficial role of MSRT in enhancing psychological and cognitive functions in children. Further, large-scale trials are warranted to ascertain the usefulness of the technique.

Mymensingh Med J. 2020 Oct;29(4):901-905.

Effect of Infant Massage in Reduction of Neonatal Jaundice

T Amin[1], A N Nur

Abstract

Infant massage is a traditional practice for newborns in some parts of the world; its beneficial effects in reduction of jaundice in the neonates are a matter of investigation. This study aims to find out the effects of massage therapy in term neonates with neonatal jaundice receiving phototherapy compared with a control group. This randomized controlled trial (RCT) includes total 100 term newborns evenly divided into the massage group and control group after obtaining informed consent and was conducted in the Neonatal ward of the Sher-e-Bangla Medical College, Barisal, Bangladesh from 1st January 2018 to 30th June 2018. The massage group received both massage therapy and phototherapy for neonatal jaundice whereas the control group received only phototherapy. Data were collected and analyzed and results were prepared by student's 't' test for continuous variables and chi-square test

for categorical variables and statistical significance was found if p value <0.05. Both the massage group and control group were comparable in birth weight, weight at admission, gestational age, sex ratio, mode of delivery and hospital stay (p>0.05). The defecation frequency was significantly more in massage group than control group and serum bilirubin levels were significantly lower in massage group than control group on day 3 onward (p<0.05). Infant massage is a safe, effective and economic practice, which can be an adjunct to phototherapy in the management of neonatal jaundice.

Community health workers and education

Cash transfers and family economic support

PLoS Med. 2020 Nov 17;17(11):e1003388.
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Evaluation of an unconditional cash transfer program targeting children's first-1,000-days linear growth in rural Togo: A cluster-randomized controlled trial

Justine Briaux[1,2], Yves Martin-Prevel[1], Sophie Carles[1], Sonia Fortin[1], Yves Kameli[1], Laura Adubra[1], Andréa Renk[3], Yawavi Agboka[4], Magali Romedenne[5], Félicité Mukantambara[6], John Van Dyck[7], Joachim Boko[8], Renaud Becquet[2], Mathilde Savy[1]

Abstract

Background: In 2014, the government of Togo implemented a pilot unconditional cash transfer (UCT) program in rural villages that aimed at improving children's nutrition, health, and protection. It combined monthly UCTs (approximately US$8.40 /month) with a package of community activities (including behavior change communication [BCC] sessions, home visits, and integrated community case management of childhood illnesses and acute malnutrition [ICCM-Nut]) delivered to mother-child pairs during the first "1,000 days" of life. We primarily investigated program impact at population level on children's height-for-age z-scores (HAZs) and secondarily on stunting (HAZ < -2) and intermediary outcomes including household's food insecurity, mother-child pairs' diet and health, delivery in a health facility and low birth weight (LBW), women's knowledge, and physical intimate partner violence (IPV).

Methods and findings: We implemented a parallel-cluster-randomized controlled trial, in which 162 villages were randomized into either an intervention arm (UCTs + package of community activities, n = 82) or a control arm (package of community activities only, n = 80). Two different representative samples of children aged 6-29 months and their mothers were surveyed in each arm, one before the intervention in 2014 (control: n = 1,301, intervention: n = 1,357), the other 2 years afterwards in 2016 (control: n = 996, intervention: n = 1,035). Difference-in-differences (DD) estimates of impact were calculated, adjusting for clustering. Children's average age was 17.4 (± 0.24 SE) months in the control arm and 17.6 (± 0.19 SE) months in the intervention arm at baseline. UCTs had a protective effect on HAZ (DD = +0.25 z-scores, 95% confidence interval [CI]: 0.01-0.50, p = 0.039), which deteriorated in the control arm while remaining stable in the intervention arm, but had no impact on stunting (DD = -6.2 percentage points [pp], relative odds ratio [ROR]: 0.74, 95% CI: 0.51-1.06, p = 0.097). UCTs

positively impacted both mothers' and children's (18-23 months) consumption of animal source foods (ASFs) (respectively, DD = +4.5 pp, ROR: 2.24, 95% CI: 1.09-4.61, p = 0.029 and DD = +9.1 pp, ROR: 2.65, 95% CI: 1.01-6.98, p = 0.048) and household food insecurity (DD = -10.7 pp, ROR: 0.63, 95% CI: 0.43-0.91, p = 0.016). UCTs did not impact on reported child morbidity 2 week's prior to report (DD = -3.5 pp, ROR: 0.80, 95% CI: 0.56-1.14, p = 0.214) but reduced the financial barrier to seeking healthcare for sick children (DD = -26.4 pp, ROR: 0.23, 95% CI: 0.08-0.66, p = 0.006). Women who received cash had higher odds of delivering in a health facility (DD = +10.6 pp, ROR: 1.53, 95% CI: 1.10-2.13, p = 0.012) and lower odds of giving birth to babies with birth weights (BWs) <2,500 g (DD = -11.8, ROR: 0.29, 95% CI: 0.10-0.82, p = 0.020). Positive effects were also found on women's knowledge (DD = +14.8, ROR: 1.86, 95% CI: 1.32-2.62, p < 0.001) and physical IPV (DD = -7.9 pp, ROR: 0.60, 95% CI: 0.36-0.99, p = 0.048). Study limitations included the short evaluation period (24 months) and the low coverage of UCTs, which might have reduced the program's impact.
Conclusions: UCTs targeting the first "1,000 days" had a protective effect on child's linear growth in rural areas of Togo. Their simultaneous positive effects on various immediate, underlying, and basic causes of malnutrition certainly contributed to this ultimate impact. The positive impacts observed on pregnancy- and birth-related outcomes call for further attention to the conception period in nutrition-sensitive programs.

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Impact of the extension of a performance-based financing scheme to nutrition services in Burundi on malnutrition prevention and management among children below five: A cluster-randomized control trial

Catherine Korachais[1], Sandra Nkurunziza[2 3], Manassé Nimpagaritse[1 4 5], Bruno Meessen[1]

Abstract
Malnutrition is a huge problem in Burundi. In order to improve the health system response, the Ministry of Health piloted the introduction of malnutrition prevention and care indicators within its performance-based financing (PBF) scheme. Paying for units of services and for qualitative indicators is expected to enhance provision and quality of these nutrition services. The objective of this study is to assess the impacts of this intervention, on both child acute malnutrition recovery rates at health centre level and prevalence of chronic and acute malnutrition among children at community level. This study follows a cluster-randomized controlled evaluation design: 90 health centres (HC) were randomly selected for the study, 45 of them were randomly assigned to the intervention and received payment related to their performance in malnutrition activities, while the other 45 constituted the control group and got a simple budget allocation. Data were collected from baseline and follow-up surveys of the 90 health centres and 6,480 households with children aged 6 to 23 months. From the respectively 1,067 and 1,402 moderate and severe acute malnutrition transcribed files and registers, findings suggest that the intervention had a positive impact on moderate acute malnutrition recovery rates (OR: 5.59, p = 0.039 -at the endline, 78% in the control group and 97% in the intervention group) but not on uncomplicated severe acute malnutrition recovery rate (OR: 1.16, p = 0.751 -at the endline, 93% in the control group and 92% in the intervention group). The intervention also had a significant increasing impact on the number of children treated for acute malnutrition. Analyses from the anthropometric

data collected among 12,679 children aged 6-23 months suggest improvements at health centre level did not translate into better results at community level: prevalence of both acute and chronic malnutrition remained high, precisely at the endline, acute and chronic malnutrition prevalence were resp. 8.80% and 49.90% in the control group and 8.70% and 52.0% in the intervention group, the differences being non-significant. PBF can contribute to a better management of malnutrition at HC level; yet, to address the huge problem of child malnutrition in Burundi, additional strategies are urgently required.

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Paying for performance to improve the delivery of health interventions in low- and middle-income countries

Karin Diaconu[1], Jennifer Falconer[1], Adrian Verbel[2], Atle Fretheim[3 4], Sophie Witter[1]

Background: There is growing interest in paying for performance (P4P) as a means to align the incentives of healthcare providers with public health goals. Rigorous evidence on the effectiveness of these strategies in improving health care and health in low- and middle-income countries (LMICs) is lacking; this is an update of the 2012 review on this topic.
Objectives: To assess the effects of paying for performance on the provision of health care and health outcomes in low- and middle-income countries.
Search methods: We searched CENTRAL, MEDLINE, Embase, and 10 other databases between April and June 2018. We also searched two trial registries, websites, online resources of international agencies, organizations and universities, and contacted experts in the field. Studies identified from rerunning searches in 2020 are under 'Studies awaiting classification.'
Selection criteria: We included randomized or non-randomized trials, controlled before-after studies, or interrupted time series studies conducted in LMICs (as defined by the World Bank in 2018). P4P refers to the transfer of money or material goods conditional on taking a measurable action or achieving a predetermined performance target. To be included, a study had to report at least one of the following outcomes: patient health outcomes, changes in targeted measures of provider performance (such as the delivery of healthcare services), unintended effects, or changes in resource use.
Data collection and analysis: We extracted data as per original review protocol and narratively synthesised findings. We used standard methodological procedures expected by Cochrane. Given diversity and variability in intervention types, patient populations, analyses and outcome reporting, we deemed meta-analysis inappropriate. We noted the range of effects associated with P4P against each outcome of interest. Based on intervention descriptions provided in documents, we classified design schemes and explored variation in effect by scheme design.
Main results: We included 59 studies: controlled before-after studies (19), non-randomized (16) or cluster randomized trials (14); and interrupted time-series studies (9). One study included both an interrupted time series and a controlled before-after study. Studies focused on a wide range of P4P interventions, including target payments and payment for outputs as modified by quality (or quality and equity assessments). Only one study assessed results-based aid. Many schemes were funded by national governments (23 studies) with the World

Bank funding most externally funded schemes (11 studies). Targeted services varied; however, most interventions focused on reproductive, maternal and child health indicators. Participants were predominantly located in public or in a mix of public, non-governmental and faith-based facilities (54 studies). P4P was assessed predominantly at health facility level, though districts and other levels were also involved. Most studies assessed the effects of P4P against a status quo control (49 studies); however, some studies assessed effects against comparator interventions (predominantly enhanced financing intended to match P4P funds (17 studies)). Four studies reported intervention effects against both comparator and status quo. Controlled before-after studies were at higher risk of bias than other study designs. However, some randomised trials were also downgraded due to risk of bias. The interrupted time-series studies provided insufficient information on other concurrent changes in the study context. P4P compared to a status quo control For health services that are specifically targeted, P4P may slightly improve health outcomes (low certainty evidence), but few studies assessed this. P4P may also improve service quality overall (low certainty evidence); and probably increases the availability of health workers, medicines and well-functioning infrastructure and equipment (moderate certainty evidence). P4P may have mixed effects on the delivery and use of services (low certainty evidence) and may have few or no distorting unintended effects on outcomes that were not targeted (low-certainty evidence), but few studies assessed these. For secondary outcomes, P4P may make little or no difference to provider absenteeism, motivation or satisfaction (low certainty evidence); but may improve patient satisfaction and acceptability (low certainty evidence); and may positively affect facility managerial autonomy (low certainty evidence). P4P probably makes little to no difference to management quality or facility governance (low certainty evidence). Impacts on equity were mixed (low certainty evidence). For health services that are untargeted, P4P probably improves some health outcomes (moderate certainty evidence); may improve the delivery, use and quality of some health services but may make little or no difference to others (low certainty evidence); and may have few or no distorting unintended effects (low certainty evidence). The effects of P4P on the availability of medicines and other resources are uncertain (very low certainty evidence). P4P compared to other strategies For health outcomes and services that are specifically targeted, P4P may make little or no difference to health outcomes (low certainty evidence), but few studies assessed this. P4P may improve service quality (low certainty evidence); and may have mixed effects on the delivery and use of health services and on the availability of equipment and medicines (low certainty evidence). For health outcomes and services that are untargeted, P4P may make little or no difference to health outcomes and to the delivery and use of health services (low certainty evidence). The effects of P4P on service quality, resource availability and unintended effects are uncertain (very low certainty evidence). Findings of subgroup analyses Results-based aid, and schemes using payment per output adjusted for service quality, appeared to yield the greatest positive effects on outcomes. However, only one study evaluated results-based aid, so the effects may be spurious. Overall, schemes adjusting both for quality of service and rewarding equitable delivery of services appeared to perform best in relation to service utilization outcomes.

Authors' conclusions: The evidence base on the impacts of P4P schemes has grown considerably, with study quality gradually increasing. P4P schemes may have mixed effects on outcomes of interest, and there is high heterogeneity in the types of schemes implemented and evaluations conducted. P4P is not a uniform intervention, but rather a range of approaches. Its effects depend on the interaction of several variables, including the

design of the intervention (e.g., who receives payments), the amount of additional funding, ancillary components (such as technical support) and contextual factors (including organizational context).

Community health and health education

Child and infant mental health

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Evaluation of a Program to Help Low-Income, Latina Mothers Help Their Children Cope With Stress

Thomas G Power[1], Guadalupe G Ramos[2], Yadira Olivera Guerrero[2], AnaMaria Diaz Martinez[3], Louise A Parker[2], SuYeon Lee[4]

Abstract

This paper describes the evaluation of a program that provides low-income Latina mothers with skills to help their children cope with stress. Based on focus groups with mothers and their school-aged children in two locations, we developed a five-week program for helping mothers identify signs of stress in their children, learn effective emotion-coaching skills, and learn how to effectively encourage their children to use coping strategies that match the controllability of the situation. We conducted a randomized controlled trial in an urban (n = 13) and rural (n = 78) location in which we randomly assigned mothers to either an intervention or a no-treatment control condition. We completed eight implementations of the program (2 in the urban sample and 6 in the rural one). To evaluate the program, we collected pre- and post-assessments of mothers' coping knowledge, emotion coaching, strategies for helping their children cope with stress, maternal self-efficacy in helping their children cope, general parenting practices, and general parenting self-efficacy. Observers assessed the fidelity of program delivery. Mothers who received the intervention, in contrast to those in the control condition, showed significant increases in their knowledge of strategies to help their children cope with stress, in reported emotion-coaching skills, and in the reported use of positive strategies for helping their children manage their behavior and emotions in stressful situations (i.e., helping their children relax and calm down, talking with their children about feelings, helping their children problem-solve, encouraging distraction, and helping their children improve their self-esteem). Post intervention, mothers reported increases in their efficacy for helping their children cope with stress. Analyses revealed no significant effects of the program on general parenting or general parenting self-efficacy, but did have the hypothesized effects on maternal knowledge, attitudes, and reported behavior. Subsequent research should examine the degree to which the program has effects over a longer time period and on children's approaches to coping with stress.

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Improving mother-infant interaction during infant feeding: A randomised controlled trial in a low-income community in South Africa

Mark Tomlinson[1,2], Stephan Rabie[1], Sarah Skeen[1], Xanthe Hunt[1], Lynne Murray[3], Peter J Cooper[3]

Background: Maternal-infant feeding interactions are a primary context for engagement between mothers and their infants, and constitute a unique space in which reciprocity, attunement and maternal sensitivity can be expressed. Increasingly, research demonstrates the importance of the psychological and social nature of the feeding context, and how it may be affected by maternal mental state, feeding skills and sensitivity. As such, feeding interactions may provide useful contexts for observations of maternal sensitivity, reflecting well on day-to-day maternal sensitivity.
Aims and objectives: This paper is a post hoc examination of the impact of an intervention on maternal sensitivity during a feeding interaction when the infants were 6 months old.
Participants: A total of 449 women consented to participate in the original intervention and were randomly assigned to the intervention or control groups. Mothers and infants were assessed during pregnancy, and then at 2, 6, 12 and 18 months of infant age. At the 6 month follow-up visit, 79% (354 out of 449) of the participants were retained. Post hoc analyses were conducted on the original sample to determine breastfeeding status. Sixty-nine percent of the women completed the feeding observation at the 6 months follow-up visit, of which 47% reported exclusively breastfeeding and 22% reported bottle-feeding.
Results: Results demonstrated that during a feeding interaction, maternal sensitivity was significantly improved among non-breastfeeding mothers who received the intervention. Particularly, maternal responsiveness to infant cues and synchronous interactions was higher among non-breastfeeding intervention mothers compared to control group mothers. The results also show that non-breastfeeding mothers who received the intervention were significantly less intrusive in their interactions with their infants.
Conclusion: The intervention had particular beneficial effects for mothers who were not breastfeeding and suggest that the intervention offered a protective effect for non-breastfeeding mothers.

Child protection and family violence

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Parenting, mental health and economic pathways to prevention of violence against children in South Africa

L Cluver[1], Y Shenderovich[2], F Meinck[3], M N Berezin[4], J Doubt[5], C L Ward[6], J Parra-Cardona[7], C Lombard[8], J M Lachman[9], C Wittesaele[10], I Wessels[11], F Gardner[12], J I Steinert[13]

Abstract

Background: Parenting programs based on social learning theory have increasing empirical evidence for reducing violence against children. Trials are primarily from high-income countries and with young children. Globally, we know little about how parenting programs work to reduce violence, with no known studies in low or middle-income countries (LMICs). This study examines mechanisms of change of a non-commercialized parenting program, Parenting for Lifelong Health for Teens, designed with the World Health Organization and UNICEF. A cluster randomized trial showed main effects on parenting and other secondary outcomes. We conducted secondary analysis of trial data to investigate five potential mediators of reduced violence against children: improved parenting, adolescent behaviour, caregiver mental health, alcohol/drug avoidance, and family economic strengthening.
Methods: The trial was implemented in rural South Africa with 40 sites, n = 552 family dyads (including adolescents aged 10-18 and primary caregivers). Intervention sites (n = 20) received the 14-session parenting program delivered by local community members, including modules on family budgeting and savings. Control sites (n = 20) received a brief informational workshop. Emotional and physical violence against children/adolescents and each potential mediator were reported by adolescents and caregivers at baseline and 9-13 months post-randomisation. Structural equation modelling was used to test simultaneous hypothesized pathways to violence reduction.
Results: Improvements in four pathways mediated reduced violence against children: 1) improved parenting practices, 2) improved caregiver mental health (reduced depression), 3) increased caregiver alcohol/drug avoidance and 4) improved family economic welfare. Improved child behaviour was not a mediator, although it was associated with less violence.
Conclusions: Simultaneously bolstering a set of family processes can reduce violence. Supporting self-care and positive coping for caregivers may be essential in challenging contexts. In countries with minimal or no economic safety nets, linking social learning parenting programs with economic strengthening skills may bring us closer to ending violence against children.

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Effectiveness of web-based distance education for parents in the prevention of emotional neglect and abuse: A randomized controlled study

Kübra Gülırmak[1], Oya Sevcan Orak[1]

Abstract
Purpose: The aim of this study was to determine the efficacy of web-based distance education for the prevention of child emotional neglect and abuse by increasing parental awareness of emotional abuse and appropriate attitudes toward child-rearing.
Design and methods: This study had a quasi-experimental, randomized controlled design. The study sample included a total of 60 parents who had taken their child to a pediatric outpatient clinic in Turkey. Of 60 parents, 30 were randomly assigned to an experimental group and 30 were randomly assigned to a control group. Data were collected using the Personal Characteristics Form, the Recognition of Emotional Maltreatment Scale (REMS) and the Parental Attitude Research Instrument (PARI). The experimental group was offered a 6-

week web-based distance education program focusing on the prevention of child emotional neglect and abuse.
Findings: There was no significant difference between the posttest scores of the experimental and control groups (P > .05). However, a significant difference was found between pretest and posttest scores of the experimental group for the REMS and its subscales and for the overprotective mothering and strict discipline subscales of the PARI (P < .05).
Conclusion: The 6-week web-based distance education has the potential to increase parental awareness of child-rearing and emotional abuse.
Practice implications: Web-based distance education has a positive effect on parenting attitudes and emotional abuse awareness levels. This form of parent education should, therefore, be utilized further in clinical practice.

Chagas disease

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Prospective, historically controlled study to evaluate the efficacy and safety of a new paediatric formulation of nifurtimox in children aged 0 to 17 years with Chagas disease one year after treatment (CHICO)
Jaime Altcheh[1], Luis Castro[2], Juan C Dib[3], Ulrike Grossmann[4], Erya Huang[5], Guillermo Moscatelli[1], Jimy José Pinto Rocha[6], Teresa Estela Ramírez[7], CHICO Study Group
Abstract
Nifurtimox is a recommended treatment for Chagas disease, but data from treated children are limited. We investigated the efficacy, safety and tolerability of nifurtimox administered as divisible, dispersible 30 mg and 120 mg tablets in children with Chagas disease. In this blinded, controlled study conducted January 2016-July 2018, 330 patients aged <18 years from 25 medical centres across three South American countries were randomised 2:1 to nifurtimox 10-20 mg/kg/day (aged <12 years) or 8-10 mg/kg/day (aged ≥12 years) for 60 days (n = 219), or for 30 days plus placebo for 30 days (n = 111) (ClinicalTrials.gov NCT02625974). The primary outcome was anti-Trypanosoma cruzi serological response (negative seroconversion or seroreduction ≥20% in mean optical density from baseline determined by two conventional enzyme-linked immunosorbent assays) at 12 months in the 60-day treatment group versus historical placebo controls. Nifurtimox for 60 days achieved negative seroconversion (n = 10) and seroreduction (n = 62) in 72 patients (serological response 32.9%; 95% confidence interval [CI] 26.4%, 39.3%, of all treated patients), confirming superiority relative to the upper 95% CI of 16% for controls. In patients aged <8 months, 10/12 treated for 60 days (83.3%) and 5/7 treated for 30 days (71.4%) achieved negative seroconversion. Overall serological response was lower for 30-day than for 60-day nifurtimox (between-treatment difference 14.0% [95% CI 3.7%, 24.2%]). The frequency of T. cruzi-positive quantitative polymerase chain reactions decreased substantially from baseline levels (60-day regimen 53.4% versus 1.4%; 30-day regimen 51.4% versus 4.5%). Study drug-related treatment-emergent adverse events (TEAEs), which were observed in 62 patients (28.3%) treated for 60 days and 29 patients (26.1%) treated for 30 days, were generally mild or

moderate and resolved without sequelae; 4.2% of all TEAEs led to nifurtimox discontinuation. Age- and weight-adjusted nifurtimox for 60 days achieved a serological response at 12 months post-treatment that was superior to historical placebo, was well tolerated and had a favourable safety profile in children with Chagas disease. Although, at 1 year serological follow-up, efficacy of the shorter nifurtimox treatment was not comparable to the 60-day treatment regimen for the overall study population, further long-term follow-up of the patients will provide important information about the progress of serological conversion in children treated with nifurtimox, as well as the potential efficacy difference between the two regimens over time.

COVID-19

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Pneumococcal Conjugate Vaccine Protection against Coronavirus-Associated Pneumonia Hospitalization in Children Living with and without HIV

Marta C Nunes[1,2], Clare L Cutland[3,2], Keith P Klugman[3], Shabir A Madhi[3,2]

Abstract

In December 2019 a new coronavirus (CoV) emerged as a human pathogen, SARS-CoV-2. There are few data on human coronavirus infections among individuals living with HIV. In this study we probed the role of pneumococcal coinfections with seasonal CoVs among children living with and without HIV hospitalized for pneumonia. We also described the prevalence and clinical manifestations of these infections. A total of 39,836 children who participated in a randomized, double-blind, placebo-controlled clinical trial on the efficacy of a 9-valent pneumococcal conjugate vaccine (PCV9) were followed for lower respiratory tract infection hospitalizations until 2 years of age. Nasopharyngeal aspirates were collected at the time of hospitalization and were screened by PCR for four seasonal CoVs. The frequency of CoV-associated pneumonia was higher in children living with HIV (19.9%) than in those without HIV (7.6%, $P < 0.001$). Serial CoV infections were detected in children living with HIV. The case fatality risk among children with CoV-associated pneumonia was higher in those living with HIV (30.4%) than without HIV (2.9%, $P = 0.001$). C-reactive protein and procalcitonin levels were elevated in 36.8% (≥40 mg/liter) and 64.7% (≥0.5 ng/ml), respectively, of the fatal cases living with HIV. Among children without HIV, there was a 64.0% (95% CI: 22.9% to 83.2%) lower incidence of CoV-associated pneumonia hospitalizations among PCV9 recipients compared to placebo recipients. These data suggest that *Streptococcus pneumoniae* infections might have a role in the development of pneumonia associated with endemic CoVs, that PCV may prevent pediatric CoV-associated hospitalization, and that children living with HIV with CoV infections develop more severe outcomes.**IMPORTANCE** SARS-CoV-2 may cause severe hospitalization, but little is known about the role of secondary bacterial infection in these severe cases, beyond the observation of high levels of reported inflammatory markers, associated with bacterial infection, such as procalcitonin. We did a secondary analysis of a double-blind randomized trial of PCV to examine its impact on human CoV infections before the pandemic. We found that both children living with and without HIV randomized to receive PCV had evidence of less hospitalization due to seasonal CoV, suggesting that pneumococcal coinfection may play a role in severe hospitalized CoV infections.

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Physical interventions to interrupt or reduce the spread of respiratory viruses

Tom Jefferson[1], Chris B Del Mar[2], Liz Dooley[2], Eliana Ferroni[3], Lubna A Al-Ansary[4], Ghada A Bawazeer[5], Mieke L van Driel[6 7], Mark A Jones[2], Sarah Thorning[8], Elaine M Beller[2], Justin Clark[2], Tammy C Hoffmann[2], Paul P Glasziou[2], John M Conly[9 10 11]

Abstract

Background: Viral epidemics or pandemics of acute respiratory infections (ARIs) pose a global threat. Examples are influenza (H1N1) caused by the H1N1pdm09 virus in 2009, severe acute respiratory syndrome (SARS) in 2003, and coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in 2019. Antiviral drugs and vaccines may be insufficient to prevent their spread. This is an update of a Cochrane Review published in 2007, 2009, 2010, and 2011. The evidence summarised in this review does not include results from studies from the current COVID-19 pandemic.

Objectives: To assess the effectiveness of physical interventions to interrupt or reduce the spread of acute respiratory viruses.

Search methods: We searched CENTRAL, PubMed, Embase, CINAHL on 1 April 2020. We searched ClinicalTrials.gov, and the WHO ICTRP on 16 March 2020. We conducted a backwards and forwards citation analysis on the newly included studies.

Selection criteria: We included randomised controlled trials (RCTs) and cluster-RCTs of trials investigating physical interventions (screening at entry ports, isolation, quarantine, physical distancing, personal protection, hand hygiene, face masks, and gargling) to prevent respiratory virus transmission. In previous versions of this review we also included observational studies. However, for this update, there were sufficient RCTs to address our study aims. DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane. We used GRADE to assess the certainty of the evidence. Three pairs of review authors independently extracted data using a standard template applied in previous versions of this review, but which was revised to reflect our focus on RCTs and cluster-RCTs for this update. We did not contact trialists for missing data due to the urgency in completing the review. We extracted data on adverse events (harms) associated with the interventions.

Main results: We included 44 new RCTs and cluster-RCTs in this update, bringing the total number of randomised trials to 67. There were no included studies conducted during the COVID-19 pandemic. Six ongoing studies were identified, of which three evaluating masks are being conducted concurrent with the COVID pandemic, and one is completed. Many studies were conducted during non-epidemic influenza periods, but several studies were conducted during the global H1N1 influenza pandemic in 2009, and others in epidemic influenza seasons up to 2016. Thus, studies were conducted in the context of lower respiratory viral circulation and transmission compared to COVID-19. The included studies were conducted in heterogeneous settings, ranging from suburban schools to hospital wards in high-income countries; crowded inner city settings in low-income countries; and an immigrant neighbourhood in a high-income country. Compliance with interventions was low in many studies. The risk of bias for the RCTs and cluster-RCTs was mostly high or unclear. Medical/surgical masks compared to no masks We included nine trials (of which eight were cluster-RCTs) comparing medical/surgical masks versus no masks to prevent the spread of

viral respiratory illness (two trials with healthcare workers and seven in the community). There is low certainty evidence from nine trials (3507 participants) that wearing a mask may make little or no difference to the outcome of influenza-like illness (ILI) compared to not wearing a mask (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.82 to 1.18. There is moderate certainty evidence that wearing a mask probably makes little or no difference to the outcome of laboratory-confirmed influenza compared to not wearing a mask (RR 0.91, 95% CI 0.66 to 1.26; 6 trials; 3005 participants). Harms were rarely measured and poorly reported. Two studies during COVID-19 plan to recruit a total of 72,000 people. One evaluates medical/surgical masks (N = 6000) (published Annals of Internal Medicine, 18 Nov 2020), and one evaluates cloth masks (N = 66,000). N95/P2 respirators compared to medical/surgical masks We pooled trials comparing N95/P2 respirators with medical/surgical masks (four in healthcare settings and one in a household setting). There is uncertainty over the effects of N95/P2 respirators when compared with medical/surgical masks on the outcomes of clinical respiratory illness (RR 0.70, 95% CI 0.45 to 1.10; very low-certainty evidence; 3 trials; 7779 participants) and ILI (RR 0.82, 95% CI 0.66 to 1.03; low-certainty evidence; 5 trials; 8407 participants). The evidence is limited by imprecision and heterogeneity for these subjective outcomes. The use of a N95/P2 respirator compared to a medical/surgical mask probably makes little or no difference for the objective and more precise outcome of laboratory-confirmed influenza infection (RR 1.10, 95% CI 0.90 to 1.34; moderate-certainty evidence; 5 trials; 8407 participants). Restricting the pooling to healthcare workers made no difference to the overall findings. Harms were poorly measured and reported, but discomfort wearing medical/surgical masks or N95/P2 respirators was mentioned in several studies. One ongoing study recruiting 576 people compares N95/P2 respirators with medical surgical masks for healthcare workers during COVID-19. Hand hygiene compared to control Settings included schools, childcare centres, homes, and offices. In a comparison of hand hygiene interventions with control (no intervention), there was a 16% relative reduction in the number of people with ARIs in the hand hygiene group (RR 0.84, 95% CI 0.82 to 0.86; 7 trials; 44,129 participants; moderate-certainty evidence), suggesting a probable benefit. When considering the more strictly defined outcomes of ILI and laboratory-confirmed influenza, the estimates of effect for ILI (RR 0.98, 95% CI 0.85 to 1.13; 10 trials; 32,641 participants; low-certainty evidence) and laboratory-confirmed influenza (RR 0.91, 95% CI 0.63 to 1.30; 8 trials; 8332 participants; low-certainty evidence) suggest the intervention made little or no difference. We pooled all 16 trials (61,372 participants) for the composite outcome of ARI or ILI or influenza, with each study only contributing once and the most comprehensive outcome reported. The pooled data showed that hand hygiene may offer a benefit with an 11% relative reduction of respiratory illness (RR 0.89, 95% CI 0.84 to 0.95; low-certainty evidence), but with high heterogeneity. Few trials measured and reported harms. There are two ongoing studies of handwashing interventions in 395 children outside of COVID-19. We identified one RCT on quarantine/physical distancing. Company employees in Japan were asked to stay at home if household members had ILI symptoms. Overall fewer people in the intervention group contracted influenza compared with workers in the control group (2.75% versus 3.18%; hazard ratio 0.80, 95% CI 0.66 to 0.97). However, those who stayed at home with their infected family members were 2.17 times more likely to be infected. We found no RCTs on eye protection, gowns and gloves, or screening at entry ports.

Authors' conclusions: The high risk of bias in the trials, variation in outcome measurement, and relatively low compliance with the interventions during the studies hamper drawing firm conclusions and generalising the findings to the current COVID-19 pandemic. There is

uncertainty about the effects of face masks. The low-moderate certainty of the evidence means our confidence in the effect estimate is limited, and that the true effect may be different from the observed estimate of the effect. The pooled results of randomised trials did not show a clear reduction in respiratory viral infection with the use of medical/surgical masks during seasonal influenza. There were no clear differences between the use of medical/surgical masks compared with N95/P2 respirators in healthcare workers when used in routine care to reduce respiratory viral infection. Hand hygiene is likely to modestly reduce the burden of respiratory illness. Harms associated with physical interventions were under-investigated. There is a need for large, well-designed RCTs addressing the effectiveness of many of these interventions in multiple settings and populations, especially in those most at risk of ARIs.

Comment: *This shows how much we have learned in 2020. There is no uncertainty about the strong effectiveness of face mask in preventing COVID-19, in a health care or public setting.*

Cryptococcal infection

Dengue

(see Vaccines - dengue)

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Efficacy of Wolbachia-Infected Mosquito Deployments for the Control of Dengue

Adi Utarini[1], Citra Indriani[1], Riris A Ahmad[1], Warsito Tantowijoyo[1], Eggi Arguni[1], M Ridwan Ansari[1], Endah Supriyati[1], D Satria Wardana[1], Yeti Meitika[1], Inggrid Ernesia[1], Indah Nurhayati[1], Equatori Prabowo[1], Bekti Andari[1], Benjamin R Green[1], Lauren Hodgson[1], Zoe Cutcher[1], Edwige Rancès[1], Peter A Ryan[1], Scott L O'Neill[1], Suzanne M Dufault[1], Stephanie K Tanamas[1], Nicholas P Jewell[1], Katherine L Anders[1], Cameron P Simmons[1], AWED Study Group

Abstract

Background: *Aedes aegypti* mosquitoes infected with the *w*Mel strain of *Wolbachia pipientis* are less susceptible than wild-type *A. aegypti* to dengue virus infection.

Methods: We conducted a cluster-randomized trial involving releases of *w*Mel-infected *A. aegypti* mosquitoes for the control of dengue in Yogyakarta, Indonesia. We randomly assigned 12 geographic clusters to receive deployments of *w*Mel-infected *A. aegypti* (intervention clusters) and 12 clusters to receive no deployments (control clusters). All clusters practiced local mosquito-control measures as usual. A test-negative design was used to assess the efficacy of the intervention. Patients with acute undifferentiated fever who presented to local primary care clinics and were 3 to 45 years of age were recruited. Laboratory testing was used to identify participants who had virologically confirmed dengue (VCD) and those who were test-negative controls. The primary end point was symptomatic VCD of any severity caused by any dengue virus serotype.

Results: After successful introgression of *w*Mel into the intervention clusters, 8144 participants were enrolled; 3721 lived in intervention clusters, and 4423 lived in control

clusters. In the intention-to-treat analysis, VCD occurred in 67 of 2905 participants (2.3%) in the intervention clusters and in 318 of 3401 (9.4%) in the control clusters (aggregate odds ratio for VCD, 0.23; 95% confidence interval [CI], 0.15 to 0.35; P = 0.004). The protective efficacy of the intervention was 77.1% (95% CI, 65.3 to 84.9) and was similar against the four dengue virus serotypes. The incidence of hospitalization for VCD was lower among participants who lived in intervention clusters (13 of 2905 participants [0.4%]) than among those who lived in control clusters (102 of 3401 [3.0%]) (protective efficacy, 86.2%; 95% CI, 66.2 to 94.3).
Conclusions: Introgression of *w*Mel into *A. aegypti* populations was effective in reducing the incidence of symptomatic dengue and resulted in fewer hospitalizations for dengue among the participants.

Early childhood development

(See also: School health programs; and Nutrition – micronutrients; Adolescent health)

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doi: 10.1542/peds.2020-002725. Epub 2020 Nov 4.
Group Sessions or Home Visits for Early Childhood Development in India: A Cluster RCT
Sally Grantham-McGregor[1], Akanksha Adya[2 3], Orazio Attanasio[4 5 6 7], Britta Augsburg[5], Jere Behrman[8], Bet Caeyers[5], Monimalika Day[3], Pamela Jervis[5 9 10], Reema Kochar[3], Prerna Makkar[11], Costas Meghir[4 5 6 7], Angus Phimister[5], Marta Rubio-Codina[12], Karishma Vats[11]
Abstract
Objectives: Poor early childhood development in low- and middle-income countries is a major public health problem. Efficacy trials have shown the potential of early childhood development interventions but scaling up is costly and challenging. Guidance on effective interventions' delivery is needed. In an open-label cluster-randomized control trial, we compared the effectiveness of weekly home visits and weekly mother-child group sessions. Both included nutritional education, whose effectiveness was tested separately.
Methods: In Odisha, India, 192 villages were randomly assigned to control, nutritional education, nutritional education and home visiting, or nutritional education and group sessions. Mothers with children aged 7 to 16 months were enrolled (*n* = 1449). Trained local women ran the two-year interventions, which comprised demonstrations and interactions and targeted improved play and nutrition. Primary outcomes, measured at baseline, midline (12 months), and endline (24 months), were child cognition, language, motor development, growth and morbidity.
Results: Home visiting and group sessions had similar positive average (intention-to-treat) impacts on cognition (home visiting: 0.324 SD, 95% confidence interval [CI]: 0.152 to 0.496, *P* = .001; group sessions: 0.281 SD, 95% CI: 0.100 to 0.463, *P* = .007) and language (home visiting: 0.239 SD, 95% CI: 0.072 to 0.407, *P* = .009; group sessions: 0.302 SD, 95% CI: 0.136 to 0.468, *P* = .001). Most benefits occurred in the first year. Nutrition-education had no benefit. There were no consistent effects on any other primary outcomes.

Conclusions: Group sessions cost $38 per child per year and were as effective on average as home visiting, which cost $135, implying an increase by a factor of 3.5 in the returns to investment with group sessions, offering a more scalable model. Impacts materialize in the first year, having important design implications.

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Parenting interventions to promote early child development in the first three years of life: A global systematic review and meta-analysis

Joshua Jeong[1], Emily E Franchett[1], Clariana V Ramos de Oliveira[1], Karima Rehmani[1], Aisha K Yousafzai[1]

Abstract

Background: Parents are the primary caregivers of young children. Responsive parent-child relationships and parental support for learning during the earliest years of life are crucial for promoting early child development (ECD). We conducted a global systematic review and meta-analysis to evaluate the effectiveness of parenting interventions on ECD and parenting outcomes.

Methods and findings: We searched MEDLINE, Embase, PsycINFO, CINAHL, Web of Science, and Global Health Library for peer-reviewed, published articles from database inception until November 15, 2020. We included randomized controlled trials (RCTs) of parenting interventions delivered during the first 3 years of life that evaluated at least 1 ECD outcome. At least 2 reviewers independently screened, extracted data, and assessed study quality from eligible studies. ECD outcomes included cognitive, language, motor, and socioemotional development, behavior problems, and attachment. Parenting outcomes included parenting knowledge, parenting practices, parent-child interactions, and parental depressive symptoms. We calculated intervention effect sizes as the standardized mean difference (SMD) and estimated pooled effect sizes for each outcome separately using robust variance estimation meta-analytic approaches. We used random-effects meta-regression models to assess potential effect modification by country-income level, child age, intervention content, duration, delivery, setting, and study quality. This review was registered with PROSPERO (CRD42018092458 and CRD42018092461). Of the 11,920 articles identified, we included 111 articles representing 102 unique RCTs. Pooled effect sizes indicated positive benefits of parenting interventions on child cognitive development (SMD = 0.32, 95% CI [confidence interval]: 0.23, 0.40, P < 0.001), language development (SMD = 0.28, 95% CI: 0.18 to 0.37, P < 0.001), motor development (SMD = 0.24, 95% CI: 0.15 to 0.32, P < 0.001), socioemotional development (SMD = 0.19, 95% CI: 0.10 to 0.28, P < 0.001), and attachment (SMD = 0.29, 95% CI: 0.18 to 0.40, P < 0.001) and reductions in behavior problems (SMD = -0.13, 95% CI: -0.18 to -0.08, P < 0.001). Positive benefits were also found on parenting knowledge (SMD = 0.56, 95% CI: 0.33 to 0.79, P < 0.001), parenting practices (SMD = 0.33, 95% CI: 0.22 to 0.44, P < 0.001), and parent-child interactions (SMD = 0.39, 95% CI: 0.24 to 0.53, P < 0.001). However, there was no significant reduction in parental depressive symptoms (SMD = -0.07, 95% CI: -0.16 to 0.02, P = 0.08). Subgroup analyses revealed significantly greater effects on child cognitive, language, and motor development, and parenting practices in low- and middle-income countries compared to high-income countries; and significantly greater effects on child

cognitive development, parenting knowledge, parenting practices, and parent-child interactions for programs that focused on responsive caregiving compared to those that did not. On the other hand, there was no clear evidence of effect modification by child age, intervention duration, delivery, setting, or study risk of bias. Study limitations include considerable unexplained heterogeneity, inadequate reporting of intervention content and implementation, and varying quality of evidence in terms of the conduct of trials and robustness of outcome measures used across studies.
Conclusions: Parenting interventions for children during the first 3 years of life are effective for improving ECD outcomes and enhancing parenting outcomes across low-, middle-, and high-income countries. Increasing implementation of effective and high-quality parenting interventions is needed globally and at scale in order to support parents and enable young children to achieve their full developmental potential.

Lancet Glob Health. 2021 Mar;9(3):e309-e319.
doi: 10.1016/S2214-109X(20)30469-1. Epub 2020 Dec 17.
Group-based parenting interventions to promote child development in rural Kenya: a multi-arm, cluster-randomised community effectiveness trial
Jill E Luoto[1], Italo Lopez Garcia[2], Frances E Aboud[3], Daisy R Singla[4], Lia C H Fernald[5], Helen O Pitchik[6], Uzaib Y Saya[2], Ronald Otieno[7], Edith Alu[7]
Abstract
Background: Early childhood development (ECD) programmes can help address early disadvantages for the 43% of children younger than 5 years in low-income and middle-income countries who have compromised development. We aimed to test the effectiveness of two group-based delivery models for an integrated ECD responsive stimulation and nutrition education intervention using Kenya's network of community health volunteers.
Methods: We implemented a multi-arm, cluster-randomised community effectiveness trial in three rural subcounties across 60 villages (clusters) in western Kenya. Eligible participants were mothers or female primary caregivers aged 15 years or older with children aged 6-24 months at enrolment. If married or in established relationships, fathers or male caregivers aged 18 years or older were also eligible. Villages were randomly assigned (1:1:1) to one of three groups: group-only delivery with 16 fortnightly sessions; mixed delivery combining 12 group sessions with four home visits; and a comparison group. Villages in the intervention groups were randomly assigned (1:1) to invite or not invite fathers and male caregivers to participate. Households were surveyed at baseline and immediately post-intervention. Assessors were masked. Primary outcomes were child cognitive and language development (score on the Bayley Scales of Infant Development third edition), socioemotional development (score on the Wolke scale), and parental stimulation (Home Observation for Measurement of the Environment inventory). Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, NCT03548558.
Findings: Between Oct 1 and Nov 12, 2018, 1152 mother-child dyads were enrolled and randomly assigned (n=376 group-only intervention, n=400 mixed-delivery intervention, n=376 comparison group). At the 11-month endline survey (Aug 5-Oct 31, 2019), 1070 households were assessed for the primary outcomes (n=346 group only, n=373 mixed delivery, n=351 comparison). Children in group-only villages had higher cognitive (effect size 0·52 SD [95% CI 0·21-0·83]), receptive language (0·42 SD [0·08-0·77]), and socioemotional

scores (0·23 SD [0·03-0·44]) than children in comparison villages at endline. Children in mixed-delivery villages had higher cognitive (0·34 SD [0·05-0·62]) and socioemotional scores (0·22 SD [0·05-0·38]) than children in comparison villages; there was no difference in language scores. Parental stimulation also improved for group-only (0·80 SD [0·49-1·11]) and mixed-delivery villages (0·77 SD [0·49-1·05]) compared with the villages in the comparison group. Including fathers in the intervention had no measurable effect on any of the primary outcomes.
Interpretation: Parenting interventions delivered by trained community health volunteers in mother-child groups can effectively promote child development in low-resource settings and have great potential for scalability.

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doi: 10.1111/desc.13113. Online ahead of print.
Promoting mother-infant relationships and underlying neural correlates: Results from a randomized controlled trial of a home-visiting program for adolescent mothers in Brazil
Fernanda Speggiorin Pereira Alarcão[1], Elizabeth Shephard[1,2], Daniel Fatori[1], Renata Amável[1], Anna Chiesa[3], Lislaine Fracolli[3], Alicia Matijasevich[4], Helena Brentani[1], Charles A Nelson[5,6], James Leckman[7], Eurípedes Constantino Miguel[1], Guilherme V Polanczyk[1]
Abstract
Poverty and teenage pregnancy are common in low-and-middle-income countries and can impede the development of healthy parent-child relationships. This study aimed to test whether a home-visiting intervention could improve early attachment relationships between adolescent mothers and their infants living in poverty in Brazil. Analyses were conducted on secondary outcomes from a randomized controlled trial (NCT0280718) testing the efficacy of a home-visiting program, Primeiros Laços, on adolescent mothers' health and parenting skills and their infants' development. Pregnant youth were randomized to intervention (n = 40) or care-as-usual (CAU, n = 40) from the first trimester of pregnancy until infants were aged 24 months. Mother-infant attachment was coded during a mother-infant interaction when the infants were aged 12 months. Electrophysiological correlates of social processing (mean amplitude of the Nc component) were measured while infants viewed facial images of the mother and a stranger at age 6 months. Infants in the intervention group were more securely attached and more involved with their mothers than those receiving CAU at 12 months. Smaller Nc amplitudes to the mother's face at 6 months were associated with better social behavior at 12 months. Our findings indicate that the Primeiros Laços Program is effective in enhancing the development of mother-infant attachment.

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doi: 10.1016/S2215-0366(20)30258-3.
Effectiveness of a peer-delivered, psychosocial intervention on maternal depression and child development at 3 years postnatal: a cluster randomised trial in Pakistan
Joanna Maselko[1], Siham Sikander[2], Elizabeth L Turner[3], Lisa M Bates[4], Ikhlaq Ahmad[5], Najia Atif[5], Victoria Baranov[6], Sonia Bhalotra[7], Amina Bibi[5], Tayyaba Bibi[5], Samina Bilal[5], Pietro Biroli[8], Esther Chung[9], John A Gallis[3], Ashley Hagaman[10], Anam Jamil[5], Katherine

LeMasters[9], Karen O'Donnell[11], Elissa Scherer[12], Maria Sharif[5], Ahmed Waqas[5], Ahmed Zaidi[5], Shaffaq Zulfiqar[5], Atif Rahman[13]

Abstract

Background: Maternal depression has a recurring course that can influence offspring outcomes. Evidence on how to treat maternal depression to improve longer-term maternal outcomes and reduce intergenerational transmission of psychopathology is scarce, particularly for task-shifted, low-intensity, and scalable psychosocial interventions. We evaluated the effects of a peer-delivered, psychosocial intervention on maternal depression and child development at 3 years postnatal.

Methods: 40 village clusters in Pakistan were randomly allocated using a computerised randomisation sequence to receive a group-based, psychosocial intervention and enhanced usual care for 36 months, or enhanced usual care alone. Pregnant women (≥18 years) were screened for moderate or severe symptoms of depression (patient health questionnaire-9 [PHQ-9] score ≥10) and were recruited into the trial (570 participants), and a cohort without depression (PHQ-9 score <10) was also enrolled (584 participants). Including the non-depressed dyads enabled us to determine how much of the excess risk due to maternal depression exposure the intervention could mitigate. Research teams responsible for identifying, obtaining consent, and recruiting trial participants were blind to the allocation status throughout the duration of the study, and principal investigators, site coordinators, statisticians, and members of the trial steering committee were also blinded to the allocation status until the analysis of 6-month data for the intervention. Primary outcomes were maternal depression symptoms and remission (PHQ-9 score <10) and child socioemotional skills (strengths and difficulties questionnaire [SDQ-TD]) at 36-months postnatal. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, NCT02658994.

Findings: From Oct 15, 2014 to Feb 25, 2016 46 village clusters were assessed for eligibility, of which 40 (including 1910 mothers were enrolled. After exclusions, 288 women were randomly assigned to the enhanced usual care group and 284 to the intervention group, and 1159 women were included in a group without prenatal depression. At 36-months postnatal, complete data were available from 889 mother-child dyads: 206 (72·5%) in the intervention group, 216 (75·3%) in the enhanced usual care group, and 467 (80·0%) women who did not have prenatal-depression. We did not observe significant outcome differences between the intervention group and the enhanced usual care group for the primary outcomes. The standardised mean difference of PHQ-9 total score was -0·13 (95% CI -0·33 to 0·07), relative risk of patient health questionnaire-9 remission was 1·00 (95% CI 0·88 to 1·14), and the SDQ-TD treatment estimate was -0·10 (95% CI -1·39 to 1·19).

Interpretation: Reduced symptom severity and high remission rates were seen across both the intervention and enhanced usual care groups, possibly masking any effects of the intervention. A multi-year, psychosocial intervention can be task-shifted via peers but might be susceptible to reductions in fidelity and dosage over time (which were not among the outcomes of this trial). Early intervention efforts might need to rely on multiple models (eg, collaborative care), be of greater intensity, and potentially targeted at mothers who are at high risk for depression to reduce the intergenerational transmission of psychopathology from mothers to children.

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doi: 10.1016/j.jpeds.2021.03.064. Online ahead of print.

Attention Test Improvements from a Cluster Randomized Controlled Trial of Caregiver Training for HIV-Exposed/Uninfected Ugandan Preschool Children

Joseph Ikekwere[1], Valentine Ucheagwu[1], Itziar Familiar-Lopez[2], Alla Sikorskii[2], Jorem Awadu[2], Julius Caesar Ojuka[3], Deborah Givon[4], Cilly Shohet[4], Bruno Giordani[1], Michael J Boivin[5]

Abstract

Objective: To report vigilance attention outcomes from a cluster randomized controlled trial of early childhood development caregiver training for perinatally HIV-exposed/uninfected preschool-age children in rural Uganda. The Early Childhood Vigilance Test (ECVT) provides a webcam recording of proportion of time a child views an animation periodically moving across a computer screen.

Study design: Sixty mothers/caregivers received biweekly year-long training sessions of the Mediational Intervention for Sensitizing Caregivers (MISC), and 59 mothers received biweekly training about nutrition, hygiene, and health care. Children were tested for attention at baseline, 6 months, and 12 months with the ECVT, in terms of proportion of time spent viewing a 6-minute animation of animals greeting the child and moving across the computer monitor screen. Time viewing the animation were scored by trained observers using ProCoder program for webcam scoring of proportion of time the child faced the animation. Mixed-effects modeling was used to compare ECVT outcomes for the 2 intervention groups.

Results: Unadjusted and adjusted (for age, sex, height, and ECVT at baseline) group differences on ECVT significantly favored the MISC arm at 6 months (P = .03; 95% CI (0.01, 0.11), effect size = 0.46) but not at 12 months. Both groups made significant gains in sustained attention across the year-long intervention (P = .021) with no significant interaction effects between time and treatment arms or sex.

Conclusions: Caregiver early childhood development training enhanced attention in at-risk Ugandan children, which can be foundational to improved working memory and learning, and perhaps related to previous language benefits reported for this cohort.

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Antenatal Depressive Symptoms and Neurodevelopment Outcomes in Children at 30 Months. A Study From South India

Susan Thomas[1], Emelia Vigil[2], Tinku Thomas[3], David C Bellinger[4], Asha Ramthal[1], Anura V Kurpad[5,6], Christopher P Duggan[5,7], Krishnamachari Srinivasan[1,8]

Abstract

Background: Prevalence of antenatal depression in low and middle income countries is high. However studies examining the association between maternal antenatal depression and early childhood development from these countries are scarce. The objective of the study was to examine the association between antenatal depressive symptoms assessed serially during pregnancy and child neurodevelopment outcomes in mother-child dyads part of a randomized control trial of maternal B12 supplementation during pregnancy.

Method: Subjects were 203 women who had participated in the placebo-controlled, randomized trial of vitamin B12 supplementation during pregnancy and 6 weeks post-

partum on whom serial assessments of depressive symptoms in each of the trimesters were available. Cognitive, receptive language, expressive language, fine motor skills and gross motor skills were assessed at 30 months using the Bayley's Scale of Infant Development-3rd edition (BSID-III). Antenatal depressive symptoms were assessed at three trimesters using the Kessler's 10 Psychological Distress Scale (K10). Women were classified into three categories: not depressed (K10 <6 in all trimesters), with intermittent depressive symptoms (K10 ≥6 in at least one trimester) and with persistent depressive symptoms (K10 score ≥6 in at least 2 trimesters).
Results: 112 (55.2%) of the women did not have depressive symptoms, 58 (28.6%) had intermittent depressive symptoms and 33 (16.2%) had persistent depressive symptoms. The children of women with intermittent antenatal depressive symptoms scored lower on the receptive language domain on BSID-III compared to children of women who were not depressed on univariate analysis, but not on bivariate regression analysis. Women with persistent depressive symptoms had lower educational attainment (p = 0.004), lower social support (p = 0.006) and used more emotional coping strategies (p = 0.005) compared to the not depressed group.
Conclusions: A significant number of women in south India had antenatal depressive symptoms. Findings from this study suggest a possible association between antenatal depressive symptoms and receptive language in children. Larger studies including women with clinical depression are needed to confirm these findings.

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doi: 10.1136/bmjgh-2021-005086.
Effect of a home-based health, nutrition and responsive stimulation intervention and conditional cash transfers on child development and growth: a cluster-randomised controlled trial in Tanzania
Christopher R Sudfeld[1,2], Lilia Bliznashka[3], Geofrey Ashery[4], Aisha K Yousafzai[3], Honorati Masanja[4]
Abstract
Introduction: Evidence on the effects of community health worker (CHW) interventions and conditional cash transfers (CCTs) on child growth and development in sub-Saharan Africa remains sparse.
Methods: We conducted a single-blind, cluster-randomised controlled trial of an integrated home-visiting health, nutrition and responsive stimulation intervention alone and in combination with CCTs to promote antenatal and child clinic attendance from 2017 to 2019 in rural Morogoro Region, Tanzania. Pregnant women and caregivers with a child <1 year of age were enrolled. Twelve villages were randomised to either (1) CHW (n=200 participants), (2) CHW+CCT (n=200) or (3) control (n=193). An intention-to-treat analysis was conducted for the primary trial outcomes of child cognitive, language and motor development assessed with the Bayley Scales of Infant and Toddler Development and child length/height-for-age z-scores (HAZ) at 18 months of follow-up.
Results: The CHW and CHW+CCT interventions had beneficial effects on child cognitive development as compared with control (standardised mean difference (SMD): 0.15, 95% CI 0.05 to 0.24, and SMD: 0.18, 95% CI 0.07 to 0.28, respectively). The CHW+CCT intervention

also had positive effects on language (SMD: 0.08, 95% CI 0.01 to 0.15) and motor (SMD: 0.16, 95% CI 0.03 to 0.28) development. Both CHW and CHW+CCT interventions had no effect on HAZ in the primary analysis; however, there were statistically significant positive effects in multivariable analyses. The CHW+CCT group (mean difference: 3.0 visits, 95% CI 2.1 to 4.0) and the CHW group (mean difference: 1.5 visits, 95% CI 0.6 to 2.5) attended greater number of child health and growth monitoring clinic visits as compared to the control group.
Conclusion: Integrated CHW home-visiting interventions can improve child cognitive development and may have positive effects on linear growth. Combining CHW with CCT may provide additional benefits on clinic visit attendance and selected child development outcomes.

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doi: 10.1136/bmjgh-2020-004307.

A holistic approach to promoting early child development: a cluster randomised trial of a group-based, multicomponent intervention in rural Bangladesh

Helen O Pitchik[1], Fahmida Tofail[2], Mahbubur Rahman[3], Fahmida Akter[3], Jesmin Sultana[3], Abul Kasham Shoab[3], Tarique Md Nurul Huda[3], Tania Jahir[3], Md Ruhul Amin[3], Md Khobair Hossain[3], Jyoti Bhushan Das[3], Esther O Chung[4], Kendra A Byrd[5], Farzana Yeasmin[3], Laura H Kwong[6], Jenna E Forsyth[6], Malay K Mridha[7], Peter J Winch[8], Stephen P Luby[9], Lia Ch Fernald[10]

Abstract
Introduction: In low- and middle-income countries, children experience multiple risks for delayed development. We evaluated a multicomponent, group-based early child development intervention including behavioural recommendations on responsive stimulation, nutrition, water, sanitation, hygiene, mental health and lead exposure prevention.
Methods: We conducted a 9-month, parallel, multiarm, cluster-randomised controlled trial in 31 rural villages in Kishoreganj District, Bangladesh. Villages were randomly allocated to: group sessions ('group'); alternating groups and home visits ('combined'); or a passive control arm. Sessions were delivered fortnightly by trained community members. The primary outcome was child stimulation (Family Care Indicators); the secondary outcome was child development (Ages and Stages Questionnaire Inventory, ASQi). Other outcomes included dietary diversity, latrine status, use of a child potty, handwashing infrastructure, caregiver mental health and knowledge of lead. Analyses were intention to treat. Data collectors were independent from implementers.
Results: In July-August 2017, 621 pregnant women and primary caregivers of children<15 months were enrolled (group n=160, combined n=160, control n=301). At endline, immediately following intervention completion (July-August 2018), 574 participants were assessed (group n=144, combined n=149, control n=281). Primary caregivers in both intervention arms participated in more play activities than control caregivers (age-adjusted means: group 4.22, 95% CI 3.97 to 4.47; combined 4.77, 4.60 to 4.96; control 3.24, 3.05 to 3.39), and provided a larger variety of play materials (age-adjusted means: group 3.63, 3.31 to 3.96; combined 3.81, 3.62 to 3.99; control 2.48, 2.34 to 2.59). Compared with the control arm, children in the group arm had higher total ASQi scores (adjusted mean difference in standardised scores: 0.39, 0.15 to 0.64), while in the combined arm scores were not significantly different from the control (0.25, -0.07 to 0.54).

Conclusion: Our findings suggest that group-based, multicomponent interventions can be effective at improving child development outcomes in rural Bangladesh, and that they have the potential to be delivered at scale.

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Short-term, medium-term and long-term effects of early parenting interventions in low- and middle-income countries: a systematic review

Joshua Jeong[1], Helen O Pitchik[2], Günther Fink[3 4]

Abstract

Introduction: Parenting interventions during early childhood are known to improve various child development outcomes immediately following programme implementation. However, less is known about whether these initial benefits are sustained over time.

Methods: We conducted a systematic literature review of parenting interventions in low- and middle-income countries (LMICs) that were delivered during the first 3 years of life and had completed a follow-up evaluation of the intervention cohort at least 1 year after the primary postintervention endpoint. We summarized intervention effects over time by child-level and parent-level outcomes as well as by timing of follow-up rounds in the short-term (1-3 years after programme completion), medium-term (4-9 years), and long-term (10+ years). We also conducted exploratory meta-analyses to compare effects on children's cognitive and behavioral development by these subgroups of follow-up rounds.

Results: We identified 24 articles reporting on seven randomised controlled trials of parenting interventions delivered during early childhood that had at least one follow-up study in seven LMICs. The majority of follow-up studies were in the short-term. Three trials conducted a medium-term follow-up evaluation, and only two trials conducted a long-term follow-up evaluation. Although trials consistently supported wide-ranging benefits on early child development outcomes immediately after programme completion, results revealed a general fading of effects on children's outcomes over time. Short-term effects were mixed, and medium-term and long-term effects were largely inconclusive. The exploratory meta-analysis on cognitive development found that pooled effects were significant at postintervention and in the short-term (albeit smaller in magnitude), but the effects were not significant in the medium-term and long-term. For behavioural development, the effects were consistently null over time.

Conclusions: There have been few longer-term follow-up studies of early parenting interventions in LMICs. Greater investments in longitudinal intervention cohorts are needed in order to gain a more comprehensive understanding of the effectiveness of parenting interventions over the life course and to improve the design of future interventions so they can have greater potential for achieving and sustaining programme benefits over time.

Acad Pediatr. May-Jun 2021;21(4):638-645.
doi: 10.1016/j.acap.2021.01.003. Epub 2021 Jan 9.

Are Benefits From a Parenting Intervention Delivered Through the Health Services Sustainable? Follow-Up of a Randomized Evaluation in Jamaica

Joanne A Smith[1], Susan M Chang[2], Florencia Lopez Boo[3], Maria de la Paz Ferro[3], Susan P Walker[2]

Abstract
Objective: An innovative low-cost parenting intervention, implemented through health services in Jamaica showed benefits to children's cognitive development at 18 months and parent's attitudes concerning childcare. We assessed the impact of the intervention on child and parent outcomes at 6 years of age.
Methods: A cluster randomized trial of 2 parenting interventions was conducted through 20 health centers in Jamaica. Interventions were implemented from age 3 to 18 months and each intervention benefited cognitive development at 18 months (effect size 0.34-0.38 standard deviation). Children were reassessed at 6 years (n = 262, 80.1% of those assessed at 18 months) to determine any benefits to cognition, behavior, and parenting behavior. Loss to follow-up was not significantly different by treatment. Inverse probability weighting and Lee bounds were used to adjust for loss to follow-up, and multilevel regression analyses conducted with random effects at the health center level.
Results: There were no significant benefits to any child outcomes at age 6 years or to parenting behavior. Results are robust using the wild cluster bootstrap procedure and using Lee bounds for attrition. The initial trial benefits were reproduced with the current sample and methods.
Conclusion: Lack of sustained benefits may be related to the initial effect size and low intensity of the intervention that ended very young at age 18 months. It may also be related to lack of initial impact on home environment and fade-out of effects in a country with near universal preschool. The findings have implications for intervention design and targeting.

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Effect of a home-visiting parenting program to promote early childhood development and prevent violence: a cluster-randomized trial in Rwanda

Sarah Kg Jensen [1], Matias Placencio-Castro [2], Shauna M Murray [1], Robert T Brennan [1,3], Simo Goshev [4], Jordan Farrar [1], Aisha Yousafzai [5], Laura B Rawlings [6], Briana Wilson [6], Emmanuel Habyarimana [7], Vincent Sezibera [8], Theresa S Betancourt [9]

Abstract
Introduction: Families living in extreme poverty require interventions to support early-childhood development (ECD) due to broad risks. This longitudinal cluster randomised trial examines the effectiveness of Sugira Muryango (SM), a home-visiting intervention linked to Rwanda's social protection system to promote ECD and reduce violence compared with usual care (UC).
Methods: Families with children aged 6-36 months were recruited in 284 geographical clusters across three districts. Cluster-level randomisation (allocated 1:1 SM:UC) was used to prevent diffusion. SM was hypothesised to improve child development, reduce violence and increase father engagement. Developmental outcomes were assessed using the Ages and Stages Questionnaire (ASQ-3) and the Malawi Development Assessment Tool (MDAT) and anthropometric assessments of growth. Violence was assessed using questions from UNICEF Multiple Indicators Cluster Survey (MICS) and Rwanda Demographic and Health Surveys (DHS). Father engagement was assessed using the Home Observation for Measurement of the Environment. Blinded enumerators conducted interviews and developmental assessments.

Results: A total of 541 SM families and 508 UC families were enrolled and included in the analyses. Study attrition (2.0% children; 9.6% caregivers) was addressed by hot deck imputation. Children in SM families improved more on gross motor (d=0.162, 95% CI 0.065 to 0.260), communication (d=0.081, 95% CI 0.005 to 0.156), problem solving (d=0.101, 95% CI 0.002 to 0.179) and personal-social development (d=0.096, 95% CI -0.015 to 0.177) on the ASQ-3. SM families showed increased father engagement (OR=1.592, 95% CI 1.069 to 2.368), decreased harsh discipline (incidence rate ratio, IRR=0.741, 95% CI 0.657 to 0.835) and intimate partner violence (IRR=0.616, 95% CI:0.458 to 0.828). There were no intervention-related improvements on MDAT or child growth.
Conclusion: Social protection programmes provide a means to deliver ECD intervention.

Matern Child Nutr. 2020 Dec;16 Suppl 3(Suppl 3):e13066.
doi: 10.1111/mcn.13066.

A complementary feeding and play intervention improves the home environment and mental development among toddlers in rural India

Sylvia Fernandez Rao[1], Margaret E Bentley[2], Nagalla Balakrishna[3], Paula Griffiths[4], Hilary Creed-Kanashiro[5], Shahnaz Vazir[1], Susan L Johnson[6]

Abstract
A cluster randomized trial design was used to test the efficacy of a behaviour change communication intervention on the quality of the home environment and infant development at 15 months of age. Children (n = 600) in rural South India were followed from 3 through 15 months of age. The control group (C group) received the standard of care, the complementary feeding group (CF group) received recommendations on complementary foods and the responsive complementary feeding and play group (RCF&P group) received recommendations on complementary foods plus skills on responsive feeding and play. The intervention was delivered in biweekly home visits to caregivers using flip charts. At postintervention, infants (n = 521) were assessed for development (Bayley-II scales) and their home environment was assessed (Home Observation for Measurement of the Environment [HOME] scale). Cluster adjusted analysis of variance showed no significant differences at baseline. The HOME score at 15 months differed by group, F(2, 38) = 6.41, P = 0.004; the CF and RCF&P groups had higher scores than the C group. Scores on subscales 'Opportunities for Variety in Daily Stimulation' and 'Caregiver Promotion of Child Development' (CPCD) were higher for the RCF&P group than for the C and CF groups. Mental development index (MDI) scores differed by group, F(2, 37) = 3.31, P = 0.04, with the RCF&P group showing higher scores than the C group (P < 0.04); no differences were noted in psychomotor development index (PDI) scores (P = 0.48). The subscales of HOME associated with MDI at 15 months were 'CPCD' and 'Cleanliness of Child' (R^2 = 0.076). 'CPCD' was also associated with PDI (R^2 = 0.039). A responsive complementary feeding and play intervention delivered through home visits benefitted children's mental development and caregiving environment at 15 months.

Diarrhoea

(See also: Vaccines and immunization - Rotavirus vaccine, Hygiene and Environmental health, Malnutrition, Dengue, Nutrition - Environmental enteric dysfunction)

Treatment of diarrhoea

Indian Pediatr. 2020 Dec 15;57(12):1114-1118.
Epub 2020 Sep 7.

Effect of Green Banana (Musa paradisiaca) on Recovery in Children With Acute Watery Diarrhea With No Dehydration : A Randomized Controlled Trial

Dhandapany Gunasekaran[1], Anandhi Chandramohan[2], Kadirvel Karthikeyan[2], Banupriya Balasubramaniam[2], Podhini Jagadeesan[2], Palanisamy Soundararajan[2]

Abstract

Background: Cooked green banana (Musa paradisiaca) has been observed to be useful in reducing the duration of diarrheal illness in children.

Objective: To evaluate whether supplementation of cooked green banana shortens the duration of diarrhea in children with acute watery diarrhea with no dehydration.

Study design: Open label randomized controlled trial.

Participants: Consecutive children aged 9 months to 5 years who presented with acute watery diarrhea within 48 hours of onset of illness with no dehydration.

Intervention: Children in the control group received standard care, while those in the intervention group received cooked green banana in addition to standard care under supervision in the hospital for 72 hours, and then continued at home until diarrhea stopped or 14th day of illness, whichever is earlier.

Outcome measures: Proportion of children who improved at 72 hours of intervention (passing formed stools with normal frequency) was considered as the primary outcome and the incidence of complications such as dehydration, persistent diarrhea and secondary lactose intolerance were evaluated as the secondary outcomes.

Results: The proportion of children who recovered within 72 hours was significantly higher (62.4%) in the green banana group compared to the control group (47.2%) [RR 1.3 (95% CI 1.05-1.7), NNT=7].The number of children with complications such as dehydration and persistent diarrhea was also signi-ficantly less in the intervention group.

Conclusion: Supplementation of cooked green banana in the diet of children with acute watery diarrhea with no dehydration hastens their recovery.

Eur Rev Med Pharmacol Sci. 2020 Sep;24(18):9675-9683.
doi: 10.26355/eurrev_202009_23057.

Protective efficacy of probiotics on the treatment of acute rotavirus diarrhea in children: an updated meta-analysis

J-B Di[1], Z-T Gai

Abstract

Objective: This meta-analysis aims to uncover the therapeutic efficacy of probiotics on acute rotavirus diarrhea (RVD) in children.

Materials and methods: Randomized controlled studies reporting therapeutic efficacy of probiotics on acute RVD in children published before 1st June 2019 were searched in PubMed, EMBASE, and Cochrane. The citations in all searched literature were manually examined. Data were extracted from eligible literature for calculating STD Mean Difference

(SMD) and its corresponding 95% confidence interval (CI). Subsequently, the association between therapeutic efficacy of probiotics and acute RVD in children was evaluated. Moreover, data were weighted by an inverse variance and analyzed by a fixed or random effect model. Heterogeneity test was applied in the enrolled literature. Sensitivity and publication bias was examined. STATA 12.0 was used for meta-analysis.
Results: A total of 19 independent Randomized Controlled Trials (RCTs) involving 1,624 children with acute RVD were enrolled in this study. Three pieces of literature were excluded through sensitivity and publication bias analyses. Data extracted from eligible literature indicated that probiotics could markedly reduce the occurrence of acute RVD in children (SMD=-0.49, 95% CI=-0.74-0.25). Subgroup analysis conducted based on ethnicity uncovered a poor therapeutic efficacy of probiotics on reducing the occurrence of acute RVD in Asian children (SMD=-0.45, 95% CI=-0.94-0.04), which was markedly significant in Caucasian children (SMD=-0.54, 95% CI=-0.78--0.30). In addition, the subgroup analysis based on the probiotic subtypes found a pronounced efficacy of both Lactobacillus acidophilus (SMD=-0.67, 95% CI=-0.92-0.42) and non-Lactobacillus acidophilus probiotic (SMD=-0.45, 95% CI=-0.77-0.14) on the occurrence of acute RVD in children.
Conclusions: Probiotics could reduce the occurrence of acute RVD in children, especially in Caucasian population. Our findings still needed to be further validated in a multi-center institution with larger sample size and more qualified data.

Benef Microbes. 2020 Aug 12;11(4):339-346.
doi: 10.3920/BM2020.0046. Epub 2020 Jul 28.
A combination of three probiotic strains for treatment of acute diarrhoea in hospitalised children: an open label, randomised controlled trial
K Chen[1], J Xin[2], G Zhang[3], H Xie[4], L Luo[4], S Yuan[1], Y Bu[4], X Yang[4], Y Ge[2], C Liu[5]
Abstract
Acute diarrhoea continues to be a leading cause of morbidity, hospitalisation, and mortality worldwide, and probiotics have been proposed as a complementary therapy in the treatment of acute diarrhoea. The goal of this study is to assess the efficacy and safety of three combined probiotic strains, *Bifidobacterium lactis* Bi-07, *Lactobacillus rhamnosus* HN001, and *Lactobacillus acidophilus* NCFM, as an adjunct to rehydration therapy in treatment of acute watery diarrhoea in hospitalised children. Eligible diarrheal children were randomised into intervention group (IG, n=96, conventional treatment for diarrhoea in combination with probiotics) and control group (CG, n=98, conventional treatment for diarrhoea without probiotics). The primary assessments of this study were duration of diarrhoea and hospital stay and improvement in diarrhoea symptoms. Significantly more children in the IG showed improvements in diarrhoea (defined as a decrease of stool frequency to no more than four times per day and an improved stool consistency within 24-48 h after the treatment) than those in the CG (96.9 vs 79.6%, P<0.05). Children supplemented with the mixed strains had a 22.5 h shorter (121.4±13.7 h vs 143.9±19.8 h) mean duration of diarrhoea and 1.2 d shorter hospital stays (5.1±1.2 d vs 6.3±1.4 d) than children only receiving the rehydration therapy (P<0.05). The prevalence of constipation of children in the IG (3.1%) was markedly lower (P<0.05) than that of children in the CG (13.3%) after treatment. In conclusion, the mixture of three probiotic strains given to children aged 1-

3 years resulted in shorter durations of diarrhoea and hospitalisation and a higher percentage of improved children.

J Paediatr Child Health. 2021 Mar;57(3):431-439.
doi: 10.1111/jpc.15243. Epub 2021 Jan 7.

Systematic review with meta-analysis: Probiotics for treating acute diarrhoea in children with dehydration

Hai-Lin Wu[1,2], Xue Zhan[1,2]

Abstract

Aim: This study aimed to evaluate the effectiveness of probiotics in treating children with acute diarrhoea and dehydration.

Methods: Medline, EMBASE, and the Cochrane Library databases were searched for relevant studies and statistical analysis was performed.

Results: A total of 17 randomised controlled trials (RCTs) involving 2861 participants met the inclusion criteria. Compared with placebo, probiotics reduced the duration of diarrhoea (12 RCTs [15, 17], n = 1907, mean difference - 21.33 h, confidence interval (CI) -29.74 to -12.91, high heterogeneity, I^2 = 86%), the duration of hospitalisation when compared with placebo (eight RCTs [19, 20], n = 1606, mean difference - 0.83 days, CI -1.53 to -0.12, high heterogeneity, I^2 = 96%) and reduced risk of diarrhoea on day 4 or more days (six RCTs [19, 20], n = 1093, risk difference - 0.13, 95% CI -0.17- -0.09, no heterogeneity).

Conclusions: Probiotics alongside rehydration therapy appear to be safe and have clear beneficial effects in shortening the duration of diarrhoea in children with acute diarrhoea and dehydration.

Health Qual Life Outcomes. 2021 Jan 6;19(1):4.
doi: 10.1186/s12955-020-01636-1.

Chinese pediatric Tuina on children with acute diarrhea: a randomized sham-controlled trial

Taoying Lu[1,2,3], Lingjia Yin[2,4], Ruoqing Chen[5], Huiyan Zhang[6], Jianxiong Cai[2], Meiling Li[7], Lin Dai[8], Conghao Zhu[9], Yongping Zhang[9], Feng Xiang[9], Li Wang[9], Lu Li[9], Lixin Wang[10], Darong Wu[11,12,13]

Abstract

Background: Pediatric Tuina has been widely used in children with acute diarrhea in China. However, due to the lack of high-quality clinical evidence, the benefit of Tuina as a therapy is not clear. We aimed to assess the effect of pediatric Tuina compared with sham Tuina as an add-on therapy in addition to usual care for 0-6-year-old children with acute diarrhea.

Methods: Eighty-six participants aged 0-6 years with acute diarrhea were randomized to receive pediatric Tuina plus usual care (n = 43) or sham Tuina plus usual care (n = 43). The primary outcomes were days of diarrhea from baseline and times of diarrhea on day 3. Secondary outcomes included a global change rating (GCR) and the number of days when the stool characteristics returned to normal. Adverse events were assessed.

Results: Pediatric Tuina was associated with a reduction in times of diarrhea on day 3 compared with sham Tuina in both ITT (crude RR, 0.73 [95% CI, 0.59-0.91]) and PP analyses

(crude RR, 0.66 [95% CI, 0.53-0.83]). However, the results were not significant when we adjusted for social demographic and clinical characteristics. No significant difference was found between groups in days of diarrhea, global change rating, or number of days when the stool characteristics returned to normal.
Conclusions: In children aged 0-6 years with acute diarrhea, pediatric Tuina showed significant effects in terms of reducing times of diarrhea compared with sham Tuina. Studies with larger sample sizes and adjusted trial designs are warranted to further evaluate the effect of pediatric Tuina therapy.

Diarrhoea prevention

(also see Hygiene and Environmental health; Water, Sanitation and Hygiene)

Trop Med Health. 2021 Mar 23;49(1):26.
doi: 10.1186/s41182-021-00315-1.
Handwashing effect on diarrheal incidence in children under 5 years old in rural eastern Ethiopia: a cluster randomized controlled trial
Ephrem Tefera Solomon[1,2], Sirak Robele Gari[3], Helmut Kloos[4], Bezatu Mengistie Alemu[5]
Abstract
Background: Handwashing with soap reduces diarrheal diseases burden considerably. However, the importance of handwashing in homes has received little attention in rural eastern Ethiopia. The effectiveness of handwashing may be reduced by lack of information on when and in what event hands must be washed, the frequency of handwashing, the individual who should wash his/her hands, and the procedure of handwashing. In these areas, indicators of adherence to handwashing are yet to be established. This study aimed at assessing the efficiency of handwashing on reducing diarrheal disease in children under 5 years old in rural kebeles of Dire Dawa, east Ethiopia.
Methods: Community-based cluster randomized controlled trial was conducted in rural kebeles of Dire Dawa for 4 months starting from October 2018 to January 2019. Selected clusters were randomized in intervention and control arms using draw method and data collectors conducted the baseline survey. Households assigned to the intervention group were given two bars of plain soap on a bi-monthly basis together with information promoting hand hygiene. Control households were allowed to continue their habitual handwashing practices. We compared the diarrheal incidences of the intervention and non-intervention households. Generalized estimation equations using Poisson family and log choice of the link was employed to calculate adjusted incidence rate ratio with its 95% confidence interval.
Results: We recorded a significant lesser diarrheal incidence in the handwashing arm than in the non-intervention arm (6.9 versus 13.8 episodes per 100 person weeks of observation). In all, there was a 41% reduction in diarrheal incidence in the intervention arm in relation to the non-intervention arm.
Conclusion: Handwashing with soap complemented with hand hygiene promotion significantly decreased diarrheal episodes in children under 5 years old in rural kebeles of Dire Dawa. We recommend the promotion and adaptation of washing hands using soap at

recommended times to be an effective means of reducing childhood diarrhea morbidity in rural populations of Ethiopia towards achieving the Sustainable Development Goal 6.

Trop Med Int Health. 2020 Aug;25(8):996-1007.
doi: 10.1111/tmi.13415. Epub 2020 Jul 21.

Diarrhoeal disease knowledge among diarrhoea patient housholds: findings from the randomised controlled trial of the Cholera-Hospital-Based-Intervention-for-7-days (CHoBI7) mobile health program

Jahed Masud[1], Md Sazzadul Islam Bhuyian[1], Shwapon Kumar Biswas[1], Fatema Zohura[1], Jamie Perin[2], Nowshin Papri[1], Fahmida Dil Farzana[1], Tahmina Parvin[1], Shirajum Monira[1], Munirul Alam[1], Christine Marie George[2]

Abstract

Objective: The objective of this study was to evaluate the impact of the Cholera-Hospital-Based-Intervention-for-7-days (CHoBI7) handwashing with soap and water treatment mobile health (mHealth) program on diarrhoeal disease knowledge among diarrhoea patients and their household members in urban Dhaka, Bangladesh.

Methods: A cluster-randomised controlled trial of the CHoBI7 mHealth program was conducted among diarrhoea patient households in Dhaka, Bangladesh. Patients were randomised to three arms: standard recommendation on oral rehydration solution use; health facility delivery of CHoBI7 plus mHealth (weekly voice and text messages) (no home visits); and health facility delivery of CHoBI7 plus two home visits and mHealth. An open-ended questionnaire was administered to 1468 participants 12 years of age or older on diarrhoeal disease transmission and prevention. These items were combined to form a diarrhoeal disease knowledge score measured at baseline and at a 1 week, 6 month and 12 month follow-up.

Results: At baseline, when participants were asked to report three ways diarrhoeal diseases were spread 37% (546/1468) of participants reported by water, 13% (187/1468) by lack of handwashing and 4% (53/1468) by food not being covered properly. At baseline when asked to name three ways diarrhoeal diseases could be prevented, 35% (515/1468) of participants reported safe water, and 16% (228/1468) reported handwashing with soap. At the 12-month follow-up, the overall diarrhoeal disease knowledge score was significantly higher in the mHealth with no home visits arm (score coefficient: 0.69, 95% Confidence Interval: 0.36, 1.01, $P < 0.0001$) and the mHealth with two home visits arm (score coefficient: 1.18, 95% CI: 0.87, 1.49, $P < 0.0001$) compared with the standard recommendation arm.

Conclusion: The CHoBI7 mHealth program significantly increased knowledge of diarrhoeal disease transmission and prevention among diarrhoea patients and their household members 12 months after in-person visits for program delivery were conducted.

Trop Med Int Health. 2020 Aug;25(8):1008-1015.
doi: 10.1111/tmi.13416. Epub 2020 Jul 14.

Effect of a water, sanitation and hygiene program on handwashing with soap among household members of diarrhoea patients in healthcare facilities in Bangladesh: a cluster-randomised controlled trial of the CHoBI7 mobile health program

Fatema Zohura[1], Md Sazzadul Islam Bhuyian[1], Ronald E Saxton[2], Tahmina Parvin[1], Shirajum Monira[1], Shwapon K Biswas[1], Jahed Masud[1], Sharika Nuzhat[1], Nowshin Papri[1], M Tasdik Hasan[1], Elizabeth D Thomas[2], David Sack[2], Jamie Perin[2], Munirul Alam[1], Christine Marie George[2]

Abstract

Objective: The Cholera-Hospital-Based-Intervention-for-7-days (CHoBI7) is a water treatment and handwashing with soap intervention for diarrhoea patients and their household members which is initially delivered in a healthcare facility setting. This study evaluated the effectiveness of CHoBI7 program delivery in increasing handwashing with soap in a healthcare facility setting among diarrhoea patients and their household members.

Methods: A randomised controlled trial of the CHoBI7 program was conducted among 404 diarrhoea patients and their accompanying household members in healthcare facilities in Dhaka, Bangladesh. The 'Standard Message' Arm received the standard message given in Bangladesh to diarrhoea patients on the use of oral rehydration solution. The 'Health Facility Visit + Soapy Water' Arm received the standard message, the CHoBI7 communication module delivered bedside to the patient; and a soapy water bottle in the healthcare facility. The 'Health Facility Visit + Handwashing Station' Arm received this same intervention plus a small plastic handwashing station. Within 24 h of intervention delivery, three-hour structured observation of handwashing practices at stool/vomit- and food-related events (key events) was conducted in healthcare facilities of diarrhoea patients and their accompanying household members.

Results: Compared to the Standard Message Arm, there was significantly more handwashing with soap at key events in both the Health Facility Visit + Soapy Water Arm (51% vs. 25 %) (Odds Ratio: 3.02; (95% Confidence Interval (CI): 1.41, 6.45) and the Health Facility Visit + Handwashing Station Arm (58% vs. 25%) OR: 4.12; (95% CI: 1.86, 9.14).

Conclusion: These findings demonstrate that delivery of the CHoBI7 communication module and provision of a soapy water bottle to diarrhoea patients and their accompanying household members presents a promising approach to increase handwashing with soap among this high risk population in a healthcare facility setting in Bangladesh.

Cochrane Database Syst Rev. 2021 Jan 6;12(1):CD004265.
doi: 10.1002/14651858.CD004265.pub4.

Hand-washing promotion for preventing diarrhoea

Regina I Ejemot-Nwadiaro[1], John E Ehiri[2], Dachi Arikpo[3], Martin M Meremikwu[4], Julia A Critchley[5]

Abstract

Background: Diarrhoea accounts for 1.8 million deaths in children in low- and middle-income countries (LMICs). One of the identified strategies to prevent diarrhoea is hand washing.

Objectives: To assess the effects of hand-washing promotion interventions on diarrhoeal episodes in children and adults.

Search methods: We searched CENTRAL, MEDLINE, Embase, nine other databases, the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP), and metaRegister of Controlled Trials (mRCT) on 8 January 2020, together with reference checking, citation searching and contact with study authors to identify additional studies.
Selection criteria: Individually-randomized controlled trials (RCTs) and cluster-RCTs that compared the effects of hand-washing interventions on diarrhoea episodes in children and adults with no intervention.
Data collection and analysis: Three review authors independently assessed trial eligibility, extracted data, and assessed risks of bias. We stratified the analyses for child day-care centres or schools, community, and hospital-based settings. Where appropriate, we pooled incidence rate ratios (IRRs) using the generic inverse variance method and a random-effects model with a 95% confidence interval (CI). We used the GRADE approach to assess the certainty of the evidence.
Main results: We included 29 RCTs: 13 trials from child day-care centres or schools in mainly high-income countries (54,471 participants), 15 community-based trials in LMICs (29,347 participants), and one hospital-based trial among people with AIDS in a high-income country (148 participants). All the trials and follow-up assessments were of short-term duration. Hand-washing promotion (education activities, sometimes with provision of soap) at child day-care facilities or schools prevent around one-third of diarrhoea episodes in high-income countries (incidence rate ratio (IRR) 0.70, 95% CI 0.58 to 0.85; 9 trials, 4664 participants, high-certainty evidence) and may prevent a similar proportion in LMICs, but only two trials from urban Egypt and Kenya have evaluated this (IRR 0.66, 95% CI 0.43 to 0.99; 2 trials, 45,380 participants; low-certainty evidence). Only four trials reported measures of behaviour change, and the methods of data collection were susceptible to bias. In one trial from the USA hand-washing behaviour was reported to improve; and in the trial from Kenya that provided free soap, hand washing did not increase, but soap use did (data not pooled; 3 trials, 1845 participants; low-certainty evidence). Hand-washing promotion among communities in LMICs probably prevents around one-quarter of diarrhoea episodes (IRR 0.71, 95% CI 0.62 to 0.81; 9 trials, 15,950 participants; moderate-certainty evidence). However, six of these nine trials were from Asian settings, with only one trial from South America and two trials from sub-Saharan Africa. In seven trials, soap was provided free alongside hand-washing education, and the overall average effect size was larger than in the two trials which did not provide soap (soap provided: RR 0.66, 95% CI 0.58 to 0.75; 7 trials, 12,646 participants; education only: RR 0.84, 95% CI 0.67 to 1.05; 2 trials, 3304 participants). There was increased hand washing at major prompts (before eating or cooking, after visiting the toilet, or cleaning the baby's bottom) and increased compliance with hand-hygiene procedure (behavioural outcome) in the intervention groups compared with the control in community trials (data not pooled: 4 trials, 3591 participants; high-certainty evidence). Hand-washing promotion for the one trial conducted in a hospital among a high-risk population showed significant reduction in mean episodes of diarrhoea (1.68 fewer) in the intervention group (mean difference -1.68, 95% CI -1.93 to -1.43; 1 trial, 148 participants; moderate-certainty evidence). Hand-washing frequency increased to seven times a day in the intervention group versus three times a day in the control arm in this hospital trial (1 trial, 148 participants; moderate-certainty evidence). We found no trials evaluating the effects of hand-washing promotions on diarrhoea-related deaths or cost effectiveness.
Authors' conclusions: Hand-washing promotion probably reduces diarrhoea episodes in both child day-care centres in high-income countries and among communities living in LMICs

by about 30%. The included trials do not provide evidence about the long-term impact of the interventions.

Ear disease and hearing loss

Ebola and viral haemorrhagic fever

Endocrine disorders and bone health

Diabetes

Bone health

Epilepsy and acute seizures

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Efficacy of low glycemic index diet therapy (LGIT) in children aged 2-8 years with drug-resistant epilepsy: A randomized controlled trial
Kannan Lakshminarayanan[1], Anuja Agarawal[2], Prateek Kumar Panda[3], Rahul Sinha[4], Manjari Tripathi[5], Ravindra M Pandey[6], Sheffali Gulati[7]
Abstract
Background: A classic ketogenic diet, even though effective in children with drug-resistant epilepsy is not tolerated well by them and cumbersome to prepare. Low glycemic index therapy (LGIT), the least restrictive with minimal adverse effects among ketogenic dietary therapies has been proven effective in uncontrolled trials, but a placebo-controlled trial in this regard is still lacking.
Methods: In this open-label randomized controlled study, we randomized children above age two years with drug-resistant epilepsy into two groups (LGIT and control groups). Patients in the LGIT group received an add-on low glycemic index diet for 3 months along with the ongoing antiepileptic drugs and the patients in the control group did not receive any dietary intervention. Seizure frequency was assessed from the seizure diary maintained by the parents. Diet compliance was assessed using the diet diary that was maintained by the parents for three days just before the scheduled monthly visits of the patients.
Results: Forty children with drug-refractory epilepsy (20 in each group) were enrolled. While 6/20 children in the LGIT arm have >50 % reduction in seizure frequency, none achieved this in the control arm (p = 0.02). The overall compliance with the low glycemic diet in the intervention group was 88.5 %. Out of six responders to LGIT, one child achieved seizure

freedom and one achieved >90 % seizure reduction. Five continued LGIT further for a median duration of 8 months (range-4-12 months) successfully. The number needed to treat for more than 50 % seizure reduction was 3 and for more than 90 % seizure reduction was 10. The mean frequency of seizures for the intervention and control groups at three months of follow-up was not significantly different (p = 0.16), but the change in seizure frequency as compared to baseline was better in the intervention arm (p = 0.01). Three patients in the LGIT arm had non-serious adverse events (lethargy in two, vomiting in one).
Conclusion: In children aged 2-8 years with drug-refractory epilepsy, the administration of LGIT along with ongoing anti-seizure medications (ASM) is more efficacious in reducing seizure frequency as compared to ASM alone.

Clin Drug Investig. 2021 Jan;41(1):1-17.doi: 10.1007/s40261-020-00975-7. Epub 2020 Nov 4.
Preferential Antiseizure Medications in Pediatric Patients with Convulsive Status Epilepticus: A Systematic Review and Network Meta-Analysis
Yihao Zhang[#1], Yingjie Liu[#2], Qiao Liao[3], Zhixiong Liu[4]
Abstract
Background and objective: The optimal choice for first- and second-line antiseizure medications for pediatric patients with convulsive status epilepticus remains ambiguous. The present study aimed to estimate the comparative effect on the efficacy and safety of different antiseizure medications in pediatric patients with status epilepticus and provide evidence for clinical practice.
Methods: We searched PubMed, EMBASE, and the Cochrane Library for eligible randomized controlled trials. Inclusion criteria included: (1) pediatric patients; (2) diagnosis of status epilepticus; and (3) randomized controlled trials. Exclusion criteria were: (1) mixed population without a pediatric subgroup analysis; (2) not status epilepticus; (3) received the study drug prior to admission; (4) sample size fewer than 30; and (5) not randomized controlled trials. Primary outcome was seizure cessation. Secondary outcomes were seizure recurrence within 24 h, respiratory depression, and admission to an intensive care unit. The hierarchy of competing antiseizure medications was presented using the surface under the cumulative ranking curve.
Results: Eight first-line antiseizure medication studies involving 1686 participants and eight second-line antiseizure medication studies involving 1711 participants were eligible for analysis. Midazolam, diazepam, lorazepam, and paraldehyde were administered as first-line antiseizure medications. Valproate, phenobarbital, phenytoin, fosphenytoin, and levetiracetam were investigated as second-line antiseizure medications. No significant differences were observed across first- and second-line antiseizure medications. Midazolam ranked the best for primary and secondary outcomes among the first-line antiseizure medications. Phenobarbital ranked the best for seizure cessation and a lower risk of admission to the intensive care unit. Valproate had superiority in preventing recurrence within 24 h. Levetiracetam had the lowest probability of developing respiratory depression.
Conclusions: This study demonstrated the hierarchy of competing interventions. Midazolam could be a better option for first-line treatment. Phenobarbital, levetiracetam, and valproate had their respective superiority in the second-line intervention. This study may provide useful information for clinical decision making under different circumstances.

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doi: 10.1111/ane.13355. Epub 2020 Oct 22.

Carbamazepine versus levetiracetam in epilepsy due to neurocysticercosis

Akhil P Santhosh[1], Manoj Kumar Goyal[2], Manish Modi[2], Parampreet S Kharbanda[2], Chirag K Ahuja[3], Naresh Tandyala[2], Nandita Prabhat[2], Rajveer Singh[2], Sahil Mehta[2], Karthik Vinay Mahesh[2]

Abstract

Background: The choice of antiepileptic drug (AED) in newly diagnosed neurocysticercosis (NCC) patients with epilepsy continues to be arbitrary. We compared efficacy and side effect profile of levetiracetam (LEV) and carbamazepine (CBZ) for the treatment of seizures in newly diagnosed patients with NCC.

Patients and methods: This was an open-labeled randomized comparative monotherapy study including newly diagnosed drug naïve patients of NCC (n = 99) presenting with seizures who were randomized in 1:1 ratio using computed generated numbers. All patients were followed up for at least six months after start of treatment. The primary outcome measure was seizure control over six months following start of AEDs.

Results: Fifteen (15.2%) patients [CBZ- 4(8.2%); LEV- 11(22%)] developed recurrence of seizures. A trend (p = 0.09) was found toward better control of seizures in CBZ compared to LEV. Two (4%) patients in LEV group and 17 (34.6%) patients in CBZ group developed drug-related minor side effects (p < 0.0001). Three patients in CBZ group needed discontinuation of therapy due to skin rash. Eleven patients who relapsed while on LEV did not have any recurrence of seizures after switching over to CBZ. Out of 3 patients who relapsed while receiving CBZ and were changed to LEV, two developed seizures during follow-up.

Conclusion: CBZ and LEV could be used as alternatives in newly diagnosed patients of NCC at the behest of minor side effects in the CBZ group.

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doi: 10.1136/archdischild-2020-319573. Online ahead of print.

Levetiracetam for convulsive status epilepticus in childhood: systematic review and meta-analysis

Ibtihal Abdelgadir[1 2], Ali Hamud[1], Ayodeji Kadri[1], Shazia Akram[1], Abdul Pullattayil[1], Anthony K Akobeng[1], Colin Powell[3 4]
Affiliations collapse

Abstract

Importance: Prolonged seizures are life-threatening emergencies associated with significant morbidity.

Objective: To determine the efficacy and safety of levetiracetam in treating convulsive status epilepticus (CSE) in childhood.

Data sources and study selections: PubMed, Embase, the Cochrane Central Register of Controlled Trials and Cumulative Index to Nursing and Allied Health Literature were searched from inception up to April 2020. Only randomised controlled trials (RCTs) that included children aged 1 month-18 years were assessed. Two reviewers performed data assessment and extraction.

Data extraction and synthesis: Ten studies out of the 20 637 citations identified were included.
Main outcomes: Cessation of seizure activities, time to cessation of seizure activities, need for rapid sequence intubation (RSI), intensive care unit (ICU) admission, recurrence of seizures at 24 hours, adverse events and all-cause mortality.
Results: We included 10 RCTs (n=1907). There was no significant difference in cessation of seizure activities when levetiracetam was compared with phenytoin (risk ratio (RR)=1.03, 95% CI 0.98 to 1.09), levetiracetam to fosphenytoin (RR=1.16, 95% CI 1.00 to 1.35) or levetiracetam to valproate (RR=1.10, 95% CI 0.94 to 1.27). No differences were found in relation to the timing of cessation of seizures for levetiracetam versus phenytoin (mean difference (MD)=-0.45, 95% CI -1.83 to 0.93), or levetiracetam versus fosphenytoin (MD=-0.70, 95% CI -4.26 to 2.86). There were no significant differences with regard to ICU admissions, adverse events, recurrence of seizure at 24 hours, RSI and all-cause mortality.
Conclusion: Levetiracetam is comparable to phenytoin, fosphenytoin and valproate as a second line treatment of paediatric CSE.

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doi: 10.1093/tropej/fmab014.

Efficacy and Safety of Levetiracetam vs. Phenytoin as Second Line Antiseizure Medication for Pediatric Convulsive Status Epilepticus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Suresh Kumar Angurana[1], Renu Suthar[2]

Abstract
Objective: To evaluate the efficacy and safety of levetiracetam (LEV) in comparison to phenytoin (PHT) as second line antiseizure medication (ASM) for Pediatric convulsive status epilepticus (SE).
Data source: PubMed, Embase, Google scholar/Google, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials.
Study selection: Randomized controlled trials (RCTs) assessing LEV and PHT as second line agent for convulsive SE in children <18 years published between 1 January 2000 and 30 November 2020.
Data extraction: The data were pooled regarding the proportion of children achieving seizure cessation within 5-60 min of completion of study drug infusion (primary outcome); and seizure cessation within 5 min, time to achieve seizure cessation, seizure recurrence between 1 to 24 h, intubation and cardiovascular instability (secondary outcomes). Data were analyzed using RevMan version 5.4 and quality analysis was done using Cochrane risk-of-bias tool. The study protocol was registered with PROSPERO.
Data synthesis: Twelve RCTs with 2293 children were included. Seizure cessation within 5-60 min was similar with both the drugs [82% in LEV vs. 77.5% in PHT, risk ratio (RR) = 1.04, 95% confidence interval (95% CI) 0.97-1.11, p = 0.30]. Seizure recurrences within 1-24 h was higher with PHT in comparison to LEV (16.6% vs. 9.7%, RR = 0.63, 95% CI 0.44-0.90, p = 0.01). Higher proportion of children in PHT group required intubation and mechanical ventilation (21.4% vs. 14.2%, RR = 0.54, 95% CI 0.30-0.98, p = 0.04). Seizure cessation within 5 min, time to

achieve seizure cessation, and cardiovascular instability were similar with both the drugs. Three RCTs were at low risk of bias and nine were at high risk of bias.
Conclusion: The efficacy of LEV is similar to PHT as second line ASM for Pediatric convulsive SE. Seizure recurrences between 1 to24 h and requirement of intubation and mechanical ventilation were significantly higher with PHT in comparison to LEV.

Cochrane Database Syst Rev. 2021 Jun 1;6(6):CD000215.
doi: 10.1002/14651858.CD000215.pub5.
Anthelmintics for people with neurocysticercosis
Edward J M Monk[1], Katharine Abba[2], Lakshmi N Ranganathan[3]
Abstract
Background: Neurocysticercosis is a parasitic infection of the central nervous system by the larval stage of the pork tapeworm and is a common cause of seizures and epilepsy in endemic areas. Anthelmintics (albendazole or praziquantel) may be given alongside supportive treatment (antiepileptics/analgesia) with the aim of killing these larvae (cysticerci), with or without corticosteroid treatment. However, there are potential adverse effects of these drugs, and the cysticerci may eventually die without directed anthelminthic treatment.
Objectives: To assess the effects of anthelmintics on people with neurocysticercosis.
Search methods: We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, the WHO ICTRP, and ClinicalTrials.gov, up to 21 October 2020.
Selection criteria: Randomized controlled trials comparing anthelmintics and supportive treatment (+/- corticosteroids) with supportive treatment alone (+/- corticosteroids) for people with neurocysticercosis.
Data collection and analysis: Two review authors independently screened the title and abstract of all articles identified by the search. We obtained full-text articles to confirm the eligibility of all studies that passed screening. One review author extracted data, which a second review author checked. Two review authors assessed the risk of bias of each trial and performed GRADE assessments. In cases of disagreement at consensus discussion stage between review authors, we consulted a third review author. We calculated risk ratios (RR) for dichotomous variables, with 95% confidence intervals (CIs) for pooled data from studies with similar interventions and outcomes.
Main results: We included 16 studies in the review. Only two studies investigated praziquantel and did not report data in a format that could contribute to meta-analysis. Most results in this review are therefore applicable to albendazole versus placebo or no anthelmintic. The aggregate analysis across all participants with neurocysticercosis did not demonstrate a difference between groups in seizure recurrence, but heterogeneity was marked (RR 0.94, 95% CI 0.78 to 1.14; 10 trials, 1054 participants; I^2 = 67%; low-certainty evidence). When stratified by participants with a single cyst or multiple cysts, pooled analysis suggests that albendazole probably improves seizure recurrence for participants with a single cyst (RR 0.61, 95% CI 0.4 to 0.91; 5 trials, 396 participants; moderate-certainty evidence). All studies contributing to this analysis recruited participants with non-viable, intraparenchymal cysts only, and most participants were children. We are uncertain whether

or not albendazole reduces seizure recurrence in participants with multiple cysts, as the certainty of the evidence is very low, although the direction of effect is towards albendazole causing harm (RR 2.05, 95% CI 1.28 to 3.31; 2 trials, 321 participants; very low-certainty evidence). This analysis included a large study containing a highly heterogeneous population that received an assessment of unclear risk for multiple 'Risk of bias' domains. Regarding radiological outcomes, albendazole probably slightly improves the complete radiological clearance of lesions (RR 1.22, 95% CI 1.07 to 1.39; 13 trials, 1324 participants; moderate-certainty evidence) and the evolution of cysts (RR 1.27, 95% CI 1.10 to 1.47; 6 trials, 434 participants; moderate-certainty evidence). More adverse events appeared to be observed in participants treated with either albendazole or praziquantel compared to those receiving placebo or no anthelmintic. The most commonly reported side effects were headache, abdominal pain, and nausea/vomiting.
Authors' conclusions: For participants with a single cyst, there was less seizure recurrence in the albendazole group compared to the placebo/no anthelmintic group. The studies contributing to this evidence only recruited participants with a non-viable intraparenchymal cyst. We are uncertain whether albendazole reduces seizure recurrence for participants with multiple cysts. We also found that albendazole probably increases radiological clearance and evolution of lesions. There were very few studies reporting praziquantel outcomes, and these findings apply to albendazole only.

Economics, equity and poverty alleviation

Fever

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doi: 10.1177/0300060521999755.
Randomised comparative trial of the efficacy of paracetamol syrup and dispersible tablets for the treatment of fever in children
Benjamin Okereke[1], Okezie Ibeleme[1], Adaobi Bisi-Onyemaechi[2]
Abstract
Objective: Fever is the most common reason for the presentation of children in the outpatient department. Paracetamol is marketed in different formulations for ease of administration to the paediatric population. These include syrups, dispersible tablets and rectal inserts. Dispersible tablets disintegrate rapidly in liquid and are subsequently taken orally, providing another oral formulation. We determined if there is a difference in the antipyretic efficacy of the syrup and the dispersible formulation of paracetamol, thereby prompting the development of the latter (another oral formulation) for use in children.
Methods: A randomised, controlled, double-blind intervention of a single dose of both formulations was given to febrile children, and their temperatures were documented twice in 30-minute intervals. Temperature changes were compared statistically.
Results: The mean temperatures at recruitment were 38.2 ± 0.5°C and 38.3 ± 0.6°C for the dispersible and syrup group, respectively. There was no significant difference between the

temperature changes at T2 (30 minutes) and T3 (60 minutes) between the two study arms. However, the temperature was significantly different at T1 (baseline), T2 and T3 within the dispersible and syrup groups.
Conclusion: The decreasing trend in temperature was similar in both groups. Both preparations produced statistically similar antipyretic effects with no reported adverse drug reaction.

Pan Afr Med J. 2020 Aug 26;36:350.
doi: 10.11604/pamj.2020.36.350.21393. eCollection 2020.
Ibuprofen versus paracetamol for treating fever in preschool children in Nigeria: a randomized clinical trial of effectiveness and safety
Ekaete Olajide Alaje[1], Ekong Emmanuel Udoh[2], Patrick Aboh Akande[3], Friday Akwagiobe Odey[4], Martin Madu Meremikwu[4]
Abstract
Introduction: fever is the primary symptom of most childhood illnesses and a cause of concern to their caregivers. The antipyretics commonly used to treat fever are ibuprofen and paracetamol. Most studies on the effectiveness of ibuprofen and paracetamol in treating fever in under-fives were conducted in Europe and North America with very few in African children. This study was aimed at assessing the effectiveness and safety of a single dose therapy of ibuprofen versus paracetamol for treating childhood fever in Nigeria.
Methods: a randomized, controlled clinical trial was conducted in the University of Calabar Teaching Hospital, in Nigeria. A total of 140 eligible children aged 6-59 months with tympanic temperature of 38°C-40°C were enrolled, and 70 of them were assigned to one arm that received a single dose of ibuprofen (10mg/kg) and 70 had paracetamol (15mg/kg). After drug administration, the children were admitted and observed in the hospital for six hours during which period a half-hourly temperature measurement and monitoring for adverse events were done.
Results: the overall result showed that ibuprofen had a better fever reducing effect compared to paracetamol. The proportion of afebrile children in the ibuprofen versus paracetamol group at 1.5-2.5 hours of administration of the drugs was statistically significant ($p = 0.04$). The adverse events of both drugs were mild and quite comparable with vomiting being the commonest.
Conclusion: ibuprofen is more effective in the treating fever in under-fives compared to paracetamol. The adverse events of both drugs were mild and comparable.

Fluid management

Health promotion

Hygiene, sanitation and environmental health

Indoor air pollution

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doi: 10.1038/s41370-021-00309-5. Online ahead of print.

The effect of clean cooking interventions on mother and child personal exposure to air pollution: results from the Ghana Randomized Air Pollution and Health Study (GRAPHS)

Steven N Chillrud[1], Kenneth Ayuurebobi Ae-Ngibise[2], Carlos F Gould[3], Seth Owusu-Agyei[2 4], Mohammed Mujtaba[2], Grace Manu[2], Katrin Burkart[5], Patrick L Kinney[6], Ashlinn Quinn[7], Darby W Jack[8], Kwaku Poku Asante[2]

Abstract

Background: Clean cooking interventions to reduce air pollution exposure from burning biomass for daily cooking and heating needs have the potential to reduce a large burden of disease globally.

Objective: The objective of this study is to evaluate the air pollution exposure impacts of a fan-assisted efficient biomass-burning cookstove and a liquefied petroleum gas (LPG) stove intervention in rural Ghana.

Methods: We randomized 1414 households in rural Ghana with pregnant mothers into a control arm (N = 526) or one of two clean cooking intervention arms: a fan-assisted efficient biomass-burning cookstove (N = 527) or an LPG stove and cylinder refills as needed (N = 361). We monitored personal maternal carbon monoxide (CO) at baseline and six times after intervention and fine particulate matter ($PM_{2.5}$) exposure twice after intervention. Children received three CO exposure monitoring sessions.

Results: We obtained 5655 48-h maternal CO exposure estimates and 1903 for children, as well as 1379 maternal $PM_{2.5}$ exposure estimates. Median baseline CO exposures in the control, improved biomass, and LPG arms were 1.17, 1.17, and 1.30 ppm, respectively. Based on a differences-in-differences approach, the LPG arm showed a 47% reduction (95% confidence interval: 34-57%) in mean 48-h CO exposure compared to the control arm. Mean maternal $PM_{2.5}$ exposure in the LPG arm was 32% lower than the control arm during the post-intervention period (52 ± 29 vs. 77 ± 44 μg/m^3). The biomass stove did not meaningfully reduce CO or $PM_{2.5}$ exposure.

Conclusions: We show that LPG interventions lowered air pollution exposure significantly compared to three-stone fires. However, post-intervention exposures still exceeded health-relevant targets.

Significance: In a large controlled trial of cleaner cooking interventions, an LPG stove and fuel intervention reduced air pollution exposure in a vulnerable population in a low-resource setting.

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Impact of the wood-burning Justa cookstove on fine particulate matter exposure: A stepped-wedge randomized trial in rural Honduras

Megan L Benka-Coker[1], Bonnie N Young[2], Joshua P Keller[3], Ethan S Walker[4], Sarah Rajkumar[2], John Volckens[5], Nicholas Good[2], Casey Quinn[2], Christian L'Orange[6], Zachary D Weller[3], Sebastian Africano[7], Anibal B Osorto Pinel[8], Jennifer L Peel[2], Maggie L Clark[9]

Abstract

Trial design: We evaluated the impact of a biomass stove intervention on fine particulate matter ($PM_{2.5}$) concentrations using an individual-level, stepped-wedge randomized trial.

Methods: We enrolled 230 women in rural Honduran households using traditional biomass stoves and randomly allocated them to one of two study arms. The Justa stove, the study intervention, was locally-sourced, wood-burning, and included an engineered combustion chamber and chimney. At each of 6 visits over 3 years, we measured 24-hour gravimetric personal and kitchen $PM_{2.5}$ concentrations. Half of the households received the intervention after Visit 2 and half after Visit 4. We conducted intent-to-treat analyses to evaluate the intervention effect using linear mixed models with log-transformed kitchen or personal $PM_{2.5}$ (separately) as the dependent variable, adjusting for time. We also compared $PM_{2.5}$ concentrations to World Health Organization (WHO) guidelines.

Results: Arms 1 and 2 each had 115 participants with 664 and 632 completed visits, respectively. Median 24-hour average personal $PM_{2.5}$ exposures were 81 µg/m^3 (25th-75th percentile: 50-141 µg/m^3) for the traditional stove condition (n=622) and 43 µg/m^3 (25th-75th percentile: 27-73 µg/m^3) for the Justa stove condition (n=585). Median 24-hour average kitchen concentrations were 178 µg/m^3 (25th-75th percentile: 69-440 µg/m^3; n=629) and 53 µg/m^3 (25th-75th percentile: 29-103 µg/m^3; n=578) for the traditional and Justa stove conditions, respectively. The Justa intervention resulted in a 32% reduction in geometric mean personal $PM_{2.5}$ (95% confidence interval [CI]: 20-43%) and a 56% reduction (95% CI: 46-65%) in geometric mean kitchen $PM_{2.5}$. During rainy and dry seasons, 53% and 41% of participants with the Justa intervention had 24-hour average personal $PM_{2.5}$ exposures below the WHO interim target-3 guideline (37.5 µg/m^3), respectively.

Conclusion: The Justa stove intervention substantially lowered personal and kitchen $PM_{2.5}$ and may be a provisional solution that is feasible for Latin American communities where cleaner fuels may not be available, affordable, or acceptable for some time.

Int J Tuberc Lung Dis. 2020 Nov 1;24(11):1172-1177.doi: 10.5588/ijtld.20.0117.

Reducing secondhand smoke exposure at home in rural areas, Thailand: a cluster randomised controlled trial

N Intarut[1], V Chongsuvivatwong[2], P Pukdeesamai[3]

Abstract

BACKGROUND: Secondhand smoke (SHS) exposure cause of morbidity and mortality, especially in non-smokers and children. This study tested the effectiveness of an intervention for reducing exposure to SHS in homes by creating smoke-free environment where 1 to 5-year old infants reside.**METHODS:** A cluster randomised controlled trial was conducted in a rural geographic area of Thailand, with 47 villages assigned to either an intervention or a comparison group. The intervention consisted of self-education and infographic material, together with 45 text messages delivered via short message service. The control group received the self-education after the intervention at 3 months. The primary outcome was assessed by parent´s self-reported in exposure to SHS in home. Multiple logistic regression was used to test the effect of the intervention.**RESULTS:** The effects of the intervention increased the likelihood of a reducing exposure to SHS at home by 1.8-fold (95%CI 1.04 to

3.11). The average number of days of SHS exposure at home (7 days) also decreased by -1.25-fold (95%CI -1.85 to -0.66) in the intervention group.**CONCLUSION:** The effectiveness of the intervention in reducing SHS exposure at home by a creating a smoke-free environment was observed to be statistically significant.

Glob Health Sci Pract. 2020 Oct 2;8(3):372-382.
doi: 10.9745/GHSP-D-20-00011. Print 2020 Oct 1.

Impact of Improved Biomass and Liquid Petroleum Gas Stoves on Birth Outcomes in Rural Nepal: Results of 2 Randomized Trials

Joanne Katz[1], James M Tielsch[2], Subarna K Khatry[3], Laxman Shrestha[4], Patrick Breysse[5], Scott L Zeger[5], Naoko Kozuki[5], William Checkley[6], Steven C LeClerq[5], Luke C Mullany[5]

Abstract

Background: Few randomized trials have assessed the impact of reducing household air pollution from biomass stoves on adverse birth outcomes in low-income countries.

Methods: Two sequential trials were conducted in rural low-lying Nepal. Trial 1 was a cluster-randomized step-wedge trial comparing traditional biomass stoves and improved biomass stoves vented with a chimney. Trial 2 was a parallel household-randomized trial comparing vented biomass stoves and liquid petroleum gas (LPG) stoves with a year's supply of gas. Kitchen particulate matter of 2.5 µm or less ($PM_{2.5}$) and carbon monoxide (CO) were assessed before and after stove installation. Prevalent and incident pregnancies were enrolled at baseline and throughout the trials. Birth anthropometry was compared across differing exposure times in pregnancy.

Results: In trial 1, the mean 20-hour kitchen $PM_{2.5}$ concentration was reduced from 1380 µg/m^3 to 936 µg/m^3. Among infants born before the intervention, mean birth weight and gestational age were 2627 g (SD=443) and 38.8 weeks (SD=3.1), and 39% were low birth weight (LBW), 22% preterm, and 55% small for gestational age (SGA). Adverse birth outcomes were not significantly different with increasing exposure to improved stoves during pregnancy. In trial 2, the mean 20-hour $PM_{2.5}$ concentration was 885 µg/m^3 in households with vented biomass and 442 µg/m^3 in those with LPG stoves. Mean birth weight was 2780 g (SD=427) and 2742 g (SD=431), among households with vented and LPG stoves, respectively. Respective percentages for LBW, SGA, and preterm were 23%, 13%, and 42% in the vented stove group and not statistically different from 31%, 17%, and 42% in the LPG group.

Conclusions: Improved biomass or LPG stoves did not reduce adverse birth outcomes. $PM_{2.5}$ and CO following improved stove installation remained well above the World Health Organization indoor air standard of 25 µg/m^3 or intermediate air quality guideline of 37.5 µg/m^3. Trials that lower indoor air pollution further are needed.

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Household air pollution exposure and associations with household characteristics among biomass cookstove users in Puno, Peru

Magdalena Fandiño-Del-Rio[1], Josiah L Kephart[2], Kendra N Williams[3], Lawrence H Moulton[4], Kyle Steenland[5], William Checkley[6], Kirsten Koehler[7], Cardiopulmonary outcomes and Household Air Pollution trial (CHAP) Trial Investigators

Abstract

Background: Household air pollution (HAP) from combustion of biomass fuel, such as wood and animal dung, is among the leading environmental risk factors for preventable disease. Close to half of the world's population relies on biomass cookstoves for their daily cooking needs. Understanding factors that affect HAP can inform measures to maximize the effectiveness of cookstove interventions in a cost-effective manner. However, the impact of kitchen and household characteristics, as well as the presence of secondary stoves, on HAP concentrations is poorly understood in Puno, Peru.

Objective: To explore how household characteristics explain variability of kitchen area concentrations and personal exposures to CO, $PM_{2.5}$ and BC from biomass cookstoves among women in rural Peru.

Methods: Household characteristics (including kitchen materials and layout, wealth, and cooking behaviors) and HAP measurements were collected from 180 households in Puno, Peru, from baseline measurements of a randomized trial. Kitchen area concentrations and personal exposures to carbon monoxide (CO), fine particulate matter ($PM_{2.5}$) and black carbon (BC) were sampled for 48 h. We implemented simple and multivariable linear regression models to determine the associations between household characteristics and both kitchen area concentration and personal exposure to each pollutant.

Results: Mean daily kitchen area concentrations and personal exposures to HAP were, on average, 48 times above World Health Organization indoor guidelines for $PM_{2.5}$. We found that roof type explained the most variability in HAP and was strongly associated with both kitchen area concentrations and personal exposures for all pollutants after adjusting for other household variables. Personal exposures were 27%-36% lower for $PM_{2.5}$, CO and BC, in households with corrugated metal roofs, compared to roofs made of natural materials (straw, totora or reed) after adjusting for other factors. Higher kitchen area concentrations were also associated with less wealth, owning more animals, or sampling during the dry season in multivariable models. Having a liquefied petroleum gas (LPG) stove and having a chimney were associated with lower personal exposures, but were not associated with kitchen area concentrations. Personal exposures were lower by 21% for $PM_{2.5}$ and 28% for CO and BC concentrations among participants who had both LPG and biomass stoves compared to those with only biomass cookstoves adjusting for other household factors.

Conclusions: Characterizing HAP within different settings can help identify effective and culturally-relevant solutions to reduce HAP exposures. We found that housing roof type is strongly related to kitchen area concentrations and personal exposures to HAP, perhaps because of greater ventilation in kitchens with metal roofs compared to those with thatch roofs. Although HAP concentrations remained above guidelines for all households, promoting use of metal roof materials and LPG stoves may be actionable interventions that can help reduce exposures to HAP in high-altitude rural Peru and similar settings.

Water, Sanitation and Hygiene

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Impact of Low-Cost Point-of-Use Water Treatment Technologies on Enteric Infections and Growth among Children in Limpopo, South Africa

Courtney L Hill[1], Kelly McCain[2 1], Mzwakhe E Nyathi[3], Joshua N Edokpayi[4], David M Kahler[5], Darwin J Operario[6], David D J Taylor[7], Natasha C Wright[8], James A Smith[1], Richard L Guerrant[6], Amidou Samie[9], Rebecca A Dillingham[6], Pascal O Bessong[9], Elizabeth T Rogawski McQuade[10 6]

Abstract

Enteric infections early in life have been associated with poor linear growth among children in low-resource settings. Point-of-use water treatment technologies provide effective and low-cost solutions to reduce exposure to enteropathogens from drinking water, but it is unknown whether the use of these technologies translates to improvements in child growth. We conducted a community-based randomized controlled trial of two water treatment technologies to estimate their effects on child growth in Limpopo, South Africa. We randomized 404 households with a child younger than 3 years to receive a silver-impregnated ceramic water filter, a silver-impregnated ceramic tablet, a safe-storage water container alone, or no intervention, and these households were followed up quarterly for 2 years. We estimated the effects of the interventions on linear and ponderal growth, enteric infections assessed by quantitative molecular diagnostics, and diarrhea prevalence. The silver-impregnated ceramic water filters and tablets consistently achieved approximately 1.2 and 3 log reductions, respectively, in total coliform bacteria in drinking water samples. However, the filters and tablets were not associated with differences in height (height-for-age *z*-score differences compared with no intervention: 0.06, 95% CI: -0.29, 0.40, and 0.00, 95% CI: -0.35, 0.35, respectively). There were also no effects of the interventions on weight, diarrhea prevalence, or enteric infections. Despite their effectiveness in treating drinking water, the use of the silver-impregnated ceramic water filters and tablets did not reduce enteric infections or improve child growth. More transformative water, sanitation, and hygiene interventions that better prevent enteric infections are likely needed to improve long-term child growth outcomes.

J Health Econ. 2021 May;77:102456.
doi: 10.1016/j.jhealeco.2021.102456. Epub 2021 Mar 31.

Sanitation, financial incentives and health spillovers: A cluster randomised trial

Lisa Cameron[1], Paulo Santos[2], Milan Thomas[3], Jeff Albert[4]

Abstract

Poor sanitation and its consequent negative health outcomes continue to plague the developing world. Drawing on the finding that financial subsidies have changed behaviour in other health contexts, we conducted a clustered randomised trial in 160 villages in Lao PDR to evaluate the effectiveness of combining financial incentives with Community-Led Total

Sanitation (CLTS), a widely-conducted behaviour change program. Villages were randomly allocated to four groups, all of which received CLTS but differed in the type of subsidy offered (none, household, village or both). Using data from a random sample of households with young children and village administrative data, we show that household incentives increased sanitation take-up among the poor, whereas a village incentive increased take-up primarily among the non-poor. Improved sanitation produced positive health spillovers - a 10 percentage point increase in village sanitation coverage decreased the probability of childhood stunting by 3 percentage points.

Environ Sci Technol. 2020 Nov 3;54(21):13828-13838.
doi: 10.1021/acs.est.0c02606. Epub 2020 Oct 20.

Ingestion of Fecal Bacteria along Multiple Pathways by Young Children in Rural Bangladesh Participating in a Cluster-Randomized Trial of Water, Sanitation, and Hygiene Interventions (WASH Benefits)

Laura H Kwong[1], Ayse Ercumen[2], Amy J Pickering[3], Joanne E Arsenault[4], Mahfuza Islam[5], Sarker M Parvez[5], Leanne Unicomb[5], Mahbubur Rahman[5], Jennifer Davis[1 6], Stephen P Luby[1]

Abstract

Quantifying the contribution of individual exposure pathways to a child's total ingestion of fecal matter could help prioritize interventions to reduce environmental enteropathy and diarrhea. This study used data on fecal contamination of drinking water, food, soil, hands, and objects and second-by-second data on children's contacts with these environmental reservoirs in rural Bangladesh to assess the relative contribution of different pathways to children's ingestion of fecal indicator bacteria and if ingestion decreased with the water, sanitation, and hygiene interventions implemented in the WASH Benefits Trial. Our model estimated that rural Bangladeshi children <36 months old consume 3.6-4.9 $\log_{10}$ most probable number *E. coli*/day. Among children <6 months, placing objects in the mouth accounted for 60% of *E. coli* ingested. For children 6-35 months old, mouthing their own hands, direct soil ingestion, and ingestion of contaminated food were the primary pathways of *E. coli* ingestion. The amount of *E. coli* ingested by children and the predominant pathways of *E. coli* ingestion were unchanged by the water, sanitation, and hygiene interventions. These results highlight contaminated soil, children's hands, food, and objects as primary pathways of *E. coli* ingestion and emphasize the value of intervening along these pathways.

Am J Trop Med Hyg. 2021 Jan;104(1):382-390.
doi: 10.4269/ajtmh.20-0215.

A Cluster Randomized Trial of the Impact of Education through Listening (a Novel Behavior Change Technique) on Household Water Treatment with Chlorine in Vihiga District, Kenya, 2010-2011

Christine E Stauber[1], Bobbie Person[2], Ronald Otieno[3], Jared Oremo[3], Katharine Schilling[2], Matthew J Hayat[1], Tracy Ayers[2], Robert Quick[2]

Abstract

Despite multiple studies demonstrating the effectiveness of household water treatment with chlorine in disinfecting water and preventing diarrhea, social marketing of this intervention

in low- and middle-income countries has resulted in only modest uptake. In a cluster randomized trial in Vihiga district, western Kenya, we compared uptake of household water treatment with chlorine among six villages served by community vendors trained in standard social marketing plus education through listening (ETL), an innovative behavior change method, and six villages served by community vendors trained in standard social marketing only. Water treatment uptake, water quality, and childhood diarrhea were measured over 6 months and compared between the two groups of villages. During the 6-month period, we found no association between ETL exposure and reported and confirmed household water treatment with chlorine. In both groups (ETL and comparison), reported use of water treatment was low and did not change during our 6-month follow-up. However, persons confirmed to have chlorinated water had improved bacteriologic water quality. Study findings suggest that ETL implementation was suboptimal, which, along with unexpected changes in the supply and price of chlorine, may have prevented an accurate assessment of the potential impact of ETL on water treatment behavior. Taken together, these observations exemplify the complexities of habits, practices, attitudes, and external factors that can create challenging conditions for implementing behavioral interventions. As a consequence, in this trial, ETL had no measurable impact on water treatment behavior.

Glob Health Promot. 2020 Oct 25;1757975920963889.
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A pilot project: handwashing educational intervention decreases incidence of respiratory and diarrheal illnesses in a rural Malawi orphanage

Lauren Rissman[1], Alexis Deavenport-Saman[2 3], Mark H Corden[3 4], Ronen Zipkin[3 4], Juan Espinoza[2 3]

Abstract

Children who live in orphanages represent a population particularly vulnerable to transmissible diseases. Handwashing interventions have proven efficacy for reducing the rate of transmission of common infectious diseases. Few studies have analyzed the delivery of health interventions for children in orphanages in sub-Saharan Africa. To address this gap, we conducted an ecological assessment and piloted a handwashing intervention in an orphanage in rural Malawi, focusing on caregiver knowledge and behaviors, child handwashing behaviors, and disease incidence. A secondary study aim was to demonstrate program feasibility for a future randomized controlled trial. Orphanage caregivers participated in a three-module educational intervention on handwashing based on WHO recommendations and workshops on how to teach the curriculum to children. Seventeen orphanage caregivers and 65 children were monitored for handwashing behavior and child disease incidence. Friedman's tests were conducted to compare changes in caregiver knowledge and behaviors. Child handwashing behaviors and surveillance of child disease incidence were measured pre- and post-intervention. There were significant increases in caregiver hand hygiene knowledge. At six months post-intervention, handwashing with soap increased significantly among caregivers ($p < 0.001$) and was observed in children. The incidence of acute respiratory infections decreased from 30% to 6% post-intervention, resulting in an 80% decrease. The incidence of diarrhea decreased from 9.2% to 6.2% post-intervention, resulting in a 33% decrease. A brief educational intervention may improve handwashing knowledge and behaviors and help to decrease the incidence of common

infectious diseases in an orphanage in rural Malawi. In addition, the caregiver uptake of the intervention demonstrated feasibility for future studies.

BMJ Open. 2020 Jul 12;10(7):e034812.
doi: 10.1136/bmjopen-2019-034812.

Effect of water, sanitation and hygiene interventions alone and combined with nutrition on child growth in low and middle income countries: a systematic review and meta-analysis

Tolesa Bekele[1 2], Patrick Rawstorne[3], Bayzidur Rahman[3]

Abstract

Objective: This study aimed to provide clarification on the benefits of water, sanitation and hygiene (WASH) alone separately and combined with nutrition in improving child growth outcomes.

Design: Systematic review and meta-analysis.

Methods: We conducted a systematic review using the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. PubMed, MEDLINE, EMBASE, Scopus, Cochrane Library, Web of Science and Science Direct were searched in May 2018 and last updated in April 2019. We included studies that reported WASH interventions alone separately or combined with nutrition. Fixed and random-effects models were used to estimate pooled effect in mean difference (MD). Heterogeneity and publication bias statistics were performed.

Results: A total of 18 studies were included: 13 cluster randomised controlled trials (RCTs) and 5 non-randomised controlled trials (non-RCTs). Non-RCTs showed effect of WASH interventions alone on height-for-age z-score (HAZ) (MD=0.14; 95% CI 0.08 to 0.21) but RCTs did not. WASH alone of non-RCTs and RCTs that were delivered over 18-60 months indicated an effect on HAZ (MD=0.04; 95% CI 0.01 to 0.08). RCTs showed an effect for children <2 years (MD=0.07; 95% CI 0.01 to 0.13). Non-RCTs of WASH alone and those that included at least two components, improved HAZ (MD=0.15; 95% CI 0.07 to 0.23) but RCTs did not. WASH alone of non-RCTs and RCTs separately or together showed no effect on weight-for-age z-score (WAZ) and weight-for-height z-score (WHZ). Combined WASH with nutrition showed an effect on HAZ (MD=0.13; 95% CI 0.08 to 0.17) and on WAZ (MD=0.09; 95% CI 0.05 to 0.13) and was borderline on WHZ.

Conclusions: WASH interventions alone improved HAZ when delivered over 18-60 months and for children <2 years. Combined WASH with nutrition showed a strong effect on HAZ and WAZ and a borderline effect on WHZ. Integrated WASH with nutrition interventions may be effective inimproving child growth outcomes.

Health worker education

Haematological disorders

(See also Anaemia and iron deficiency, Malaria: treatment of uncomplicated malaria for study in sickle-cell disease patients)

Indian Pediatr. 2021 Mar 15;58(3):229-232.

Intravenous Acetaminophen vs Intravenous Diclofenac Sodium in Management of Skeletal Vaso-occlusive Crisis Among Children with Homozygous Sickle Cell Disease: A Randomized Controlled Trial

Prakash Chandra Panda[1], Nihar Ranjan Mishra[2], Chandra Sekhar Patra[1], Bijan Kumar Nayak[1], Smita Kumari Panda[3]

Objective: To compare the efficacy of intravenous acetaminophen and intravenous diclofenac sodium in the management of skeletal vaso-occlusive crisis among children with sickle cell disease.
Design: Single blind randomized controlled trial.
Setting: Tertiary care hospital.
Participants: 104 children with sickle cell disease and skeletal vaso-occlusive crisis.
Intervention: Intravenous acetaminophen at 10mg/kg/dose 8 hourly and intravenous diclofenac sodium at 1mg/kg/dose 8 hourly in 1:1 ratio.
Main outcome measures: Reduction in pain score (50%), number of doses needed to relieve pain after 24 hours of drug administration and decrease in pain score at 1 hour.
Results: A 50% reduction in pain score was seen in 35 (77.3%) and 10 (21.7%) children among acetaminophen and diclofenac sodium groups respectively (RR, 95% CI 3.6; 2.02-6.33, P< 0.001). The mean (SD) fall in pain score at 1 hour was significantly higher among intervention arm as compared to control arm [1.51 (0.5) and 1.06 (0.5); P<0.001]. Eight (17.4%) patients developed local phlebitis at the site of infusion among diclofenac group.
Conclusions: Intravenous acetaminophen is a better alternative to intravenous diclofenac in children with skeletal vaso-occlusive crisis.

Lancet Haematol. 2021 May;8(5):e334-e343.
doi: 10.1016/S2352-3026(21)00053-3.

Sevuparin for the treatment of acute pain crisis in patients with sickle cell disease: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

Bart J Biemond[1], Anil Tombak[2], Yurdanur Kilinc[3], Murtadha Al-Khabori[4], Miguel Abboud[5], Mohammed Nafea[6], Adlette Inati[7], Yasser Wali[4], Jens Kristensen[8], Jan Kowalski[8], Ellen Donnelly[8], John Ohd[8], TVOC01 Investigators Group

Abstract
Background: There are no approved treatments for vaso-occlusive crises in sickle cell disease. Sevuparin is a novel non-anticoagulant low molecular weight heparinoid, with anti-adhesive properties. In this study, we tested whether sevuparin could shorten vaso-occlusive crisis duration in hospitalised patients with sickle cell disease.
Methods: We did a multicentre, double-blinded, placebo-controlled, phase 2 study in 16 public access clinical hospitals in the Netherlands, Lebanon, Turkey, Bahrain, Oman, Saudi Arabia, and Jamaica. Patients aged 12-50 years with a diagnosis of sickle cell disease (types HbSS, HbSC, HbSβ^0-thalassaemia, or HbSβ^+-thalassaemia) on a stable dose of hydroxyurea,

hospitalised with vaso-occlusive crisis for parenteral opioid analgesia with a projected stay of more than 48 h were included in the study. Patients were randomly assigned (1:1) using a computer-generated randomisation scheme to receive sevuparin (18 mg/kg per day) or placebo (NaCl, 0·9% solution) intravenously for 2-7 days until vaso-occlusive crisis resolution. All individuals involved in the trial were masked to treatment allocation. The analysis was done in the intention-to-treat population. The primary endpoint was time to vaso-occlusive crisis resolution defined as freedom from parenteral opioid use (in preceding 6-10 h); and readiness for discharge as judged by the patient or physician. The trial is registered with ClinicalTrials.gov, NCT02515838.

Findings: Between Oct 7, 2015, and Feb 10, 2019, 144 patients were randomly assigned and administered sevuparin (n=69) or placebo (n=75). The median age was 22·2 years (range 12·2-33·6), 104 (72%) 144 were adults (18 years or older), and 90 (63%) were male and 54 (37%) were female. The intention-to-treat analysis for the primary endpoint showed no significant difference in median time to vaso-occlusive crisis resolution between the sevuparin and placebo groups (100·4 h [95% CI 85·5-116·8]) vs 86·4 h [70·6-95·1]; hazard ratio 0·89 [0·6-1·3]; p=0·55). Serious adverse events occurred in 16 (22%) of 68 patients in the sevuparin group and in 21 (22%) of patients in the placebo group. The most frequent treatment-emergent adverse events were pyrexia (17 [25%] in the sevuparin group vs 17 [22%] in the placebo group), constipation (12 [18%] vs 17 [22%]), and decreased haemoglobin (18 [26%] vs 9 [12%]). There were no deaths in the sevuparin group and there was one (1%) death in the placebo group after a hyper-haemolytic episode due to alloimmunisation.

Interpretation: This result, as well as the results seen in other clinical studies of inhibitors of adhesion in sickle cell disease, suggest that selectin-mediated adhesion might be important in the initiation, but not maintenance of vaso-occlusion, indicating that strategies to treat vaso-occlusive crises differ from strategies to prevent this complication.

Lancet Haematol. 2021 May;8(5):e323-e333.
doi: 10.1016/S2352-3026(21)00059-4. Epub 2021 Apr 7.

Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial

Jo Howard[1], Kenneth I Ataga[2], Robert C Brown[3], Maureen Achebe[4], Videlis Nduba[5], Amal El-Beshlawy[6], Hoda Hassab[7], Irene Agodoa[8], Margaret Tonda[8], Sarah Gray[8], Joshua Lehrer-Graiwer[8], Elliott Vichinsky[9]

Abstract

Background: For decades, patients with sickle cell disease have had only a limited number of therapies available. In 2019, voxelotor (1500 mg), an oral once-daily sickle haemoglobin polymerisation inhibitor, was approved in the USA for the treatment of sickle cell disease in patients aged 12 years and older on the basis of HOPE trial data. To further describe the applicability of voxelotor as a treatment for this chronic illness, we report the long-term efficacy and safety of this drug at 72 weeks of treatment; the conclusion of the placebo-controlled HOPE trial.

Methods: HOPE is an international, randomised, double-blind, placebo-controlled, phase 3 trial done at 60 clinical sites in Canada, Egypt, France, Italy, Jamaica, Kenya, Lebanon, Netherlands, Oman, Turkey, the USA, and the UK. Patients (aged 12-65 years) with confirmed sickle cell disease, a haemoglobin concentration of 5·5-10·5 g/dL at enrolment, and who had between one and ten vaso-occlusive crisis events in the previous 12 months were enrolled.

Patients receiving regularly scheduled transfusion therapy, who had received a transfusion in the previous 60 days, or who had been admitted to hospital for a vaso-occlusive crisis in the previous 14 days were excluded. Patients were randomly assigned (1:1:1) to receive either once-daily oral voxelotor 1500 mg, voxelotor 900 mg, or placebo for 72 weeks. Randomisation was done centrally by use of an interactive web response system, stratified by baseline hydroxyurea use (yes vs no), age group (adolescents [12 to <18 years] vs adults [18 to 65 years]), and geographic region (North America vs Europe vs other). The primary endpoint (already reported) was the proportion of patients who achieved a haemoglobin response at week 24. In this final analysis, we report prespecified long-term efficacy assessments by intention to treat, including changes in haemoglobin concentrations from baseline to week 72, changes in the concentration of haemolysis markers (absolute and percentage reticulocytes, indirect bilirubin concentrations, and lactate dehydrogenase concentrations) from baseline to week 72, the annualised incidence of vaso-occlusive crises, and patient functioning, as assessed with the Clinical Global Impression of Change (CGI-C) scale. Safety was assessed in patients who received at least one dose of treatment (modified intention-to-treat population). This trial is registered with ClinicalTrials.gov, NCT03036813.
Findings: Between Dec 5, 2016, and May 3, 2018, 449 patients were screened, of whom 274 were randomly assigned to the voxelotor 1500 mg group (n=90), the voxelotor 900 mg group (n=92), or the placebo group (n=92). At week 72, the adjusted mean change in haemoglobin concentration from baseline was 1·0 g/dL (95% CI 0·7 to -1·3) in the voxelotor 1500 mg group, 0·5 g/dL (0·3 to -0·8) in the voxelotor 900 mg group, and 0·0 g/dL (-0·3 to 0·3) in the placebo group, with a significant difference observed between the voxelotor 1500 mg group and the placebo group (p<0·0001), and between the voxelotor 900 mg group and the placebo group (p=0·014). Significant improvements in markers of haemolysis, as assessed by the difference in adjusted mean percentage change from baseline at week 72 versus placebo, were observed in the voxelotor 1500 mg group in indirect bilirubin concentrations (-26·6% [95% CI -40·2 to -12·9]) and percentage of reticulocytes (-18·6% [-33·9 to -3·3]). The proportion of patients in the voxelotor 1500 mg group who were rated as "moderately improved" or "very much improved" at week 72 with the CGI-C was significantly greater than in the placebo group (39 [74%] of 53 vs 24 [47%] of 51; p=0·0057). Serious adverse events unrelated to sickle cell disease were reported in 25 (28%) of 88 patients in the voxelotor 1500 mg group, 20 (22%) of 92 patients in the voxelotor 900 mg group, and 23 (25%) of 91 patients in the placebo group. Grade 3 or 4 adverse events were infrequent (ie, occurred in <10% of patients); anaemia occurred in five or more patients (two [2%] patients in the voxelotor 1500 mg group, seven [8%] patients in the voxelotor 900 mg group, and three [3%] patients in the placebo group). Of all 274 patients, six (2%) deaths occurred during the study (two deaths in each treatment group), all of which were judged as unrelated to treatment.
Interpretation: Voxelotor 1500 mg resulted in rapid and durable improvements in haemoglobin concentrations maintained over 72 weeks and has potential to address the substantial morbidity associated with haemolytic anaemia in sickle cell disease.

Cochrane Database Syst Rev. 2020 Sep 25;9(9):CD004448.
doi: 10.1002/14651858.CD004448.pub7.
Phytomedicines (medicines derived from plants) for sickle cell disease

Oluseyi Oniyangi[1], Damian H Cohall[2]

Abstract

Background: Sickle cell disease, a common recessively inherited haemoglobin disorder, affects people from sub-Saharan Africa, the Middle East, Mediterranean basin, Indian subcontinent, Caribbean and South America. It is associated with complications and a reduced life expectancy. Phytomedicines (medicine derived from plants in their original state) encompass many of the plant remedies from traditional healers which the populations most affected would encounter. Laboratory research and limited clinical trials have suggested positive effects of phytomedicines both in vivo and in vitro. However, there has been little systematic appraisal of their benefits. This is an updated version of a previously published Cochrane Review.

Objectives: To assess the benefits and risks of phytomedicines in people with sickle cell disease of all types, of any age, in any setting.

Search methods: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register, the International Standard Randomised Controlled Trial Number Register (ISRCTN), the Allied and Complimentary Medicine Database (AMED), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Dates of most recent searches: Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register: 17 March 2020; ISRCTN: 19 April 2020; AMED: 18 May 2020; ClinicalTrials.gov: 24 April 2020; and the WHO ICTRP: 27 July 2017.

Selection criteria: Randomised or quasi-randomised trials with participants of all ages with sickle cell disease, in all settings, comparing the administration of phytomedicines, by any mode to placebo or conventional treatment, including blood transfusion and hydroxyurea.

Data collection and analysis: Both authors independently assessed trial quality and extracted data.

Main results: Three trials (212 participants) of three phytomedicines: Niprisan® (also known as Nicosan®), Ciklavit® and a powdered extract of Pfaffia paniculata were included. The Phase IIB (pivotal) trial suggests that Niprisan® may be effective in reducing episodes of severe painful sickle cell disease crisis over a six-month period (low-quality evidence). It did not appear to affect the risk of severe complications or the level of anaemia (low-quality evidence). The single trial of Cajanus cajan (Ciklavit®) reported a possible benefit to individuals with painful crises, and a possible adverse effect (non-significant) on the level of anaemia (low-quality evidence). We are uncertain of the effect of Pfaffia paniculata on the laboratory parameters and symptoms of SCD (very low-quality of evidence). No adverse effects were reported with Niprisan® and Pfaffia paniculata (low- to very low-quality evidence).

Authors' conclusions: While Niprisan® appeared to be safe and effective in reducing severe painful crises over a six-month follow-up period, further trials are required to assess its role in managing people with SCD and the results of its multicentre trials are awaited. Currently, no conclusions can be made regarding the efficacy of Ciklavit® and the powdered root extract of Pfaffia paniculata in managing SCD. Based on the published results for Niprisan® and in view of the limitations in data collection and analysis of the three trials, phytomedicines may have a potential beneficial effect in reducing painful crises in SCD. This needs to be further validated in future trials. More trials with improved study design and data collection are required on the safety and efficacy of phytomedicines used in managing SCD.

Am J Hematol. 2021 Jan;96(1):89-97.
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Randomized control trial of oral arginine therapy for children with sickle cell anemia hospitalized for pain in Nigeria

Richard Onalo[1,2], Peter Cooper[2], Antoinette Cilliers[3], Barend C Vorster[4], Nnebe-Agumadu Uche[1], Oniyangi O Oluseyi[5], Victoria D Onalo[6], Yunusa Zubairu[6], Alice U Ayodele-Kehinde[7], Oladimeji M Damilare[8], Janet Figueroa[9], Claudia R Morris[10,11]

Abstract

Low arginine bioavailability is associated with vaso-occlusive painful crisis (VOC) severity in sickle cell anemia (SCA) and predicts need for pediatric hospitalization. Intravenous arginine therapy has opioid-sparing effects and was found to significantly decrease pain scores in children hospitalized with SCA-VOC in a phase-two randomized placebo-controlled trial (RCT). Efficacy of oral arginine is unknown. Our objective was to determine the safety and efficacy of oral arginine therapy in Nigerian children with SCA. A double-blind RCT of oral L-arginine-hydrochloride (100 mg/kg TID) was conducted in children with SCA-VOC, aged 5-17 years, hospitalized at two Nigerian sites. The primary outcome measure was analgesic usage, quantified by difference in the mean Analgesic Medication Quantification Scale (MQS). Secondary outcomes included daily pain scores, time-to-crisis-resolution and length-of-hospital-stay. An intention-to-treat analysis was performed. Sixty-eight children (age 5-17 years, mean 10.6 ± 0.4 years; 56% male), were randomized to receive L-arginine (35 patients) or placebo (33 patients). The mean total MQS for the arginine group was 73.4 (95% CI, 62.4-84.3) vs 120.0 (96.7-143.3) for placebo (P < .001). The mean rate of decline in worst pain scores was faster in the arginine arm vs placebo (1.50 [1.23-1.77] vs 1.09 [0.94-1.24] point/d, P = .009). Children receiving arginine had a shorter time-to-crisis-resolution (P = .02), shorter hospital-stay (P = .002) and experienced no serious adverse event. Pain control was more rapid, total analgesic requirement was significantly reduced, and most notably, time-to-crisis-resolution and length-of-hospital-stay were shorter in children with SCA-VOC receiving arginine vs placebo. Given the established safety and low cost, oral arginine is a promising adjuvant therapy for SCA-VOC management.

Saudi J Med Med Sci. Jan-Apr 2021;9(1):3-9.
doi: 10.4103/sjmms.sjmms_218_20. Epub 2020 Dec 26.

Ketamine for Sickle Cell Vaso-Occlusive Crises: A Systematic Review

Mohammed S Alshahrani[1], Mohannad A Alghamdi[1]

Abstract

Introduction: Vaso-occlusive crisis (VOC) is one of the main causes of hospital admission in patients with sickle cell disease (SCD). Ketamine is often used as an adjuvant to opioids to control sickle cell crisis; however, there is a lack of evidence about its safety and efficacy for VOC in SCD patients.

Objective: To synthesize evidence from published reports about the efficacy and safety of ketamine in the management of acute painful VOC in both pediatric and adult SCD patients.

Methods: A systematic literature search of PubMed, Scopus, Web of Science, EBSCO and Cochrane Library was conducted, up to March 2019. Studies reporting the analgesic effects

and side effects of ketamine in the management of acute painful VOC in pediatric and adult SCD patients were included. The primary outcome measure was improvement in pain scale, and the secondary outcomes were reduction in opioid utilization and side effects. Studies were narratively summarized in this review.
Results: Fourteen studies (with a total of 604 patients) were included in the final analysis. Several case reports and case series showed that ketamine significantly reduced pain scales and opioid utilization in both populations. The only randomized controlled trial available showed that ketamine was noninferior to morphine in reducing pain scores, but had a higher incidence of nonlife-threatening, reversible adverse effects. However, a retrospective study of 33 patients showed a higher pain score in the ketamine group with an acceptable short-term adverse effect.
Conclusion: Ketamine has a potentially comparable efficacy with other opioids in reducing the pain during VOC in SCD patients. However, it also likely has a higher rate of transient adverse events. Owing to the lack of published randomized controlled trials, current evidence is not sufficient to confirm the safety and efficacy of ketamine. Future well-designed randomized controlled trials are strongly recommended.

BMC Nutr. 2021 Mar 18;7(1):9.
doi: 10.1186/s40795-021-00410-w.
Nutritional perspectives on sickle cell disease in Africa: a systematic review
Eunice Berko Nartey[1 2], Jonathan Spector[3], Seth Adu-Afarwuah[4], Catherine L Jones[5], Alan Jackson[6], Agartha Ohemeng[4], Rajiv Shah[7], Alice Koryo-Dabrah[8], Amma Benneh-Akwasi Kuma[9], Hyacinth I Hyacinth[10 11], Matilda Steiner-Asiedu[4]
Abstract
Background: Sickle cell disease (SCD) is an inherited blood disorder that predominantly affects individuals in sub-Saharan Africa. However, research that elucidates links between SCD pathophysiology and nutritional status in African patients is lacking. This systematic review aimed to assess the landscape of studies in sub-Saharan Africa that focused on nutritional aspects of SCD, and highlights gaps in knowledge that could inform priority-setting for future research.
Methods: The study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Inclusion criteria comprised original, peer-reviewed research published between January 1995 and November 2020 involving individuals in Africa with any phenotypic variant of SCD and at least one nutritional status outcome. Nutritional status outcomes were defined as those that assessed dietary intakes, growth/anthropometry, or nutritional biomarkers. Databases used were Ovid Embase, Medline, Biosis and Web of Science.
Results: The search returned 526 articles, of which 76 were included in the final analyses. Most investigations (67%) were conducted in Nigeria. Studies were categorized into one of three main categories: descriptive studies of anthropometric characteristics (49%), descriptive studies of macro- or micronutrient status (41%), and interventional studies (11%). Findings consistently included growth impairment, especially among children and adolescents from sub-Saharan Africa. Studies assessing macro- and micronutrients generally had small sample sizes and were exploratory in nature. Only four randomized trials were

identified, which measured the impact of lime juice, long-chain fatty acids supplementation, ready-to-use supplementary food (RUSF), and oral arginine on health outcomes.
Conclusions: The findings reveal a moderate number of descriptive studies, most with small sample sizes, that focused on various aspects of nutrition and SCD in African patients. There was a stark dearth of interventional studies that could be used to inform evidence-based changes in clinical practice. Findings from the investigations were generally consistent with data from other regional settings, describing a significant risk of growth faltering and malnutrition among individuals with SCD. There is an unmet need for clinical research to better understand the potential benefits of nutrition-related interventions for patients with SCD in sub-Saharan Africa to promote optimal growth and improve health outcomes.

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doi: 10.1371/journal.pone.0246700. eCollection 2021.
Evidence-based interventions implemented in low-and middle-income countries for sickle cell disease management: A systematic review of randomized controlled trials
Joyce Gyamfi[1], Temitope Ojo[2], Sabrina Epou[1], Amy Diawara[1], Lotanna Dike[1], Deborah Adenikinju[1], Scholastica Enechukwu[1], Dorice Vieira[3], Obiageli Nnodu[4], Gbenga Ogedegbe[5], Emmanuel Peprah[1 2]
Abstract
Background: Despite ~90% of sickle cell disease (SCD) occurring in low-and middle-income countries (LMICs), the vast majority of people are not receiving evidence-based interventions (EBIs) to reduce SCD-related adverse outcomes and mortality, and data on implementation research outcomes (IROs) and SCD is limited. This study aims to synthesize available data on EBIs for SCD and assess IROs.
Methods: We conducted a systematic review of RCTs reporting on EBIs for SCD management implemented in LMICs. We identified articles from PubMed/Medline, Global Health, PubMed Central, Embase, Web of Science medical subject heading (MeSH and Emtree) and keywords, published from inception through February 23, 2020, and conducted an updated search through December 24, 2020. We provide intervention characteristics for each study, EBI impact on SCD, and evidence of reporting on IROs.
Main results: 29 RCTs were analyzed. EBIs identified included disease modifying agents, supportive care agents/analgesics, anti-malarials, systemic treatments, patient/ provider education, and nutritional supplements. Studies using disease modifying agents, nutritional supplements, and anti-malarials reported improvements in pain crisis, hospitalization, children's growth and reduction in severity and prevalence of malaria. Two studies reported on the sustainability of supplementary arginine, citrulline, and daily chloroquine and hydroxyurea for SCD patients. Only 13 studies (44.8%) provided descriptions that captured at least three of the eight IROs. There was limited reporting of acceptability, feasibility, fidelity, cost and sustainability.
Conclusion: EBIs are effective for SCD management in LMICs; however, measurement of IROs is scarce. Future research should focus on penetration of EBIs to inform evidence-based practice and sustainability in the context of LMICs.

Heart disease

Rheumatic heart disease

Congenital heart disease and cardiac surgery

J Card Surg. 2020 Dec;35(12):3302-3309.
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Benefits of perioperative sildenafil therapy in children with a ventricular septal defect with pulmonary artery hypertension on early surgical outcomes

Ruchit Patel[1], Shyam Kumar Singh Thingnam[1], Anand Kumar Mishra[1], Manoj Kumar Rohit[2], Vinay Upadhyay[1], Vikram Halder[1], Vidur Bansal[1]

Abstract

Objectives: Pulmonary hypertension is a common association in children with nonrestrictive ventricular septal defect. It increases perioperative mortality and morbidity. Oral sildenafil is an effective pulmonary vasodilator. In this study, we assessed effects of perioperative oral sildenafil therapy on pulmonary artery pressure and early surgical outcomes.

Methods: This was a single centre, prospective randomized control study. Thirty children with nonrestrictive ventricular septal defects with pulmonary hypertension were divided into two groups. In the sildenafil group (n = 15, mean age 23.3 months), oral sildenafil was administered two weeks before surgery. In the control group (n = 15, mean age 36 months), preoperative sildenafil was not given. Sildenafil was continued postoperatively in both groups, provided the postoperative pulmonary artery pressure was over 50% of systemic pressure.

Results: There was no perioperative mortality, pulmonary hypertensive crisis and there were no intolerable side effects related to sildenafil in either group. Mean pulmonary artery pressure showed a reduction in both groups. Sildenafil group showed statistically significant improvement in duration of cardiopulmonary bypass (100.27 ± 21.09 min vs. 125.40 ± 26.83 min, p = .008), mechanical ventilation requirement (22.79 ± 17.13 h vs. 30.53 ± 13.05 h; p = .04), epinephrine requirement (22% patients vs. 48% patients; p = .03) and hospital stay (6.13 ± 1.40 days vs. 7.53 ± 1.92 days; p = .05).

Conclusion: Oral Sildenafil therapy is an inexpensive and well-tolerated method for reducing pulmonary hypertension secondary to non-restrictive ventricular septal defect. It has noteworthy advantages regarding early surgical outcomes like reduced cardiopulmonary bypass time, improved mechanical ventilation time, lower inotrope requirement and shorter hospital stay if used preoperatively in select patient population.

Rev Fac Cien Med Univ Nac Cordoba. 2020 Dec 1;77(4):249-253.doi: 10.31053/1853.0605.v77.n4.27936.

Efficacy of citrulline supplementation to decrease the risk of pulmonary hypertension after congenital heart disease surgery. A local experience

Silene Silvera Ruiz[1], Carola L Grosso[2], Margot Tablada[3], Marcelo Cabrera[4], Raquel Dodelson de Kremer[5], Ernesto Juaneda[6], Laura E Laróvere[7]

Abstract

Introduction: Pulmonary hypertension (PH) is a major cause of morbi-mortality among patients with congenital heart disease (CHD) and also a potentially severe complication after surgical repair. Oral citrulline, a precursor to NO synthesis, is safe and efficacious for decreasing the risk of postoperative PH. Objective:

Objetive: The aim of the present study was to investigate in pediatric patients the changes of plasma citrulline, arginine, homocysteine and nitric oxide (NO) metabolites and pulmonary artery pressures (PAP) pre-post cardiac surgery in order to describe our population status with regard to the risk of pulmonary hypertension and look for potential biomarkers for early detection and treatment.

Main results/discussion: 16 Argentine pediatric patients with CHD undergoing cardiopulmonary bypass were randomized in two groups: (A) with and (B) without perioperative citrulline supplementation. We found that plasma citrulline median levels before surgery were lower in both groups respect to referential values, probably due to the poor nutritional status of our patients; only group A surpassed post-surgery the minimum recommended level to avoid PH. Furthermore, none of the patients in group A showed mean PAP higher than 20 mmHg, whereas in group B, 67% of the measurements were ≥ than the reference level.

Conclusions: We reaffirm that citrulline supplementation it is effective in reducing postoperative pulmonary hypertension and biomarkers could evidence patient status as a translational medicine application.

Nutrition. 2021 Apr;84:111027.
doi: 10.1016/j.nut.2020.111027. Epub 2020 Sep 30.

Perioperative nutritional prehabilitation in malnourished children with congenital heart disease: A randomized controlled trial

Mona Moustafa El-Ganzoury[1], Rania A El-Farrash[2], Gihan Fouad Ahmed[3], Samah Ibrahim Hassan[4], Noha M Barakat[1]

Abstract

Objective: The poor preoperative nutritional state of children with congenital heart disease (CHD) is often exacerbated postoperatively. The aim of this study was to evaluate the effect of perioperative 1- versus 2-wk nutritional prehabilitation programs on growth and surgical outcomes in malnourished children with CHD.

Methods: Forty malnourished infants scheduled for elective CHD surgery were randomized to receive either 1 or 2 wk of a nutritional prehabilitation program. Pre- and postoperative anthropometric parameters and feeding characteristics, feeding tolerance, duration of mechanical ventilation, intensive care unit (ICU) length of stay (LOS) and total hospital LOS were documented.

Results: The 2-wk prehabilitation group showed higher weight-for-age z-score and body mass index than the 1-wk group both preoperatively postnutritional, and postoperatively with significantly higher weight gain postoperatively. The 2-wk prehabilitation group had a shorter duration of postoperative mechanical ventilation, ICU LOS, and total hospital LOS.

Conclusion: The 2-wk prehabilitation program was associated with better anthropometric measurements, shorter ICU LOS postoperatively, and shorter duration of hospitalization and mechanical ventilation. The preoperative nutritional status of children with CHD had a negative effect on ICU LOS and duration of mechanical ventilation.

HIV / AIDS

Antiretroviral therapy (ART)

SAHARA J. 2021 Dec;18(1):17-25.
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Maternal and infant antiretroviral therapy adherence among women living with HIV in rural South Africa: a cluster randomised trial of the role of male partner participation on adherence and PMTCT uptake

Deborah L Jones[1], Violeta J Rodriguez[1,2], Manasi Soni Parrish[1], Tae Kyoung Lee[3], Stephen M Weiss[1], Shandir Ramlagan[4], Karl Peltzer[5,6]

Abstract

'Mother-to-child transmission of HIV' can occur during the period of pregnancy, childbirth, or breastfeeding. 'Prevention of mother-to-child transmission of HIV' (PMTCT) in Mpumalanga Province, South Africa, is especially vital as the prevalence of HIV is 28.2% in women aged 15-49. PMTCT interventions resulted in a drop of MTCT rates in Mpumalanga from ~2% in 2015 to 1.3% in 2016. This randomised controlled trial in Mpumalanga examined the potential impact of a lay healthcare worker administered intervention, 'Protect Your Family', on maternal and infant adherence, and to assess the relative influence of male partner involvement on infant and maternal adherence. This cluster randomised controlled trial used a two-phase and two-condition (experimental or control) study design where participants (*n* = 1399) did assessments both during pregnancy and post-postpartum. Only women participated in Phase 1, and both female and male partners participated in Phase 2. Results indicated that male involvement was associated with self-reported maternal or infant antiretroviral therapy (ART) adherence, but the intervention was not associated with ART adherence. Self-reported adherence was associated with depression, age, and partner HIV status. The study results provide support for the involvement of men in the antenatal clinic setting during pregnancy. Results also support further research on the meaning and assessment of male involvement and clarification of the constructs underlying the concept in the sub-Saharan African context. Outcomes provide support for male involvement and treatment of depression as adjuncts to improve uptake of both maternal and infant medication as part of the PMTCT protocol.

Medicine (Baltimore). 2020 Sep 25;99(39):e22352.
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Antiretroviral treatment and its impact on oral health outcomes in 5 to 7 year old Ugandan children: A 6 year follow-up visit from the ANRS 12174 randomized trial

Nancy Birungi[1], Lars T Fadnes[2,3], Ingunn M S Engebretsen[4], James K Tumwine[5], Anne Nordrehaug Åstrøm[1], for ANRS 12174 AND 12341 study groups

Abstract

Background: Antiretroviral therapy for HIV in sub-Saharan Africa has transformed the highly infectious virus to a stable chronic condition, with the advent of Highly active antiretroviral therapy (HAART). The longterm effects of HAART on the oral health of children are understudied.

Objective: To compare the effect of lopinavir-ritonavir and lamivudine on oral health indicators (dental caries, gingivitis, tooth eruption, and oral health related quality of life) in 5 to 7 year old HIV-1 exposed uninfected children from the ANRS 12174 trial.

Methods: This study used data collected in 2017 among children aged 5 to 7 years from the Ugandan site of the ANRS 12174 randomized trial (ClinicalTrials.gov no: NCT00640263) implemented between 2009 and 2012 in Mbale district, Eastern Uganda. The intervention was lopinavir-ritonavir or lamuvudine treatment to prevent vertical HIV-1 transmission. One hundred thirty-seven and 139 children were randomized to receive lopinavir-ritonavir or lamivudine treatment at day 7 postpartum to compare efficacy of prevention of vertical HIV-1 transmission. At follow up, the children underwent oral examination using the World Health Organization methods for field conditions. The oral health related quality of life was assessed using the early childhood oral health impact scale. Negative binomial and logistic regression were used for the analysis of data.

Main outcome measures: Dental caries, gingivitis, tooth eruption, and oral health related quality of life) in 5 to 7 year old HIV-1 exposed uninfected children.

Results: The prevalence of dental caries was 48% in the study sample: 49% in the lopinavir-ritonavir arm and 48% in the lamivudine treatment group. The corresponding mean decayed missing filled teeth and standard deviation was 1.7 (2.4) and 2.3 (3.7) The mean number (standard deviation) of erupted permanent teeth was 3.8 (3.7) and 4.6 (3.9) teeth in the lopinavir- and lamivudine group, respectively. The prevalence of reported impacts on oral health was 7% in the lopinavir-ritonavir and 18% in the lamivudine group. Gingivitis had a prevalence of 7% in the lopinavir-ritonavir and 14% lamivudine treatment group. The regression analysis revealed 70% less reported impacts on oral health in lopinavir-ritonavir group than the lamivudine treatment group with an incidence rate ratio of 0.3 (95% confidence interval: 0.1-0.9).

Conclusions: HIV exposed uninfected infants in the lopinavir-ritonavir group reported less impacts on oral health than the lamivudine treatment group. Dental caries, gingivitis, and tooth eruption were not significantly affected by the treatment lopinavir-ritonavir or lamivudine

BMC Infect Dis. 2021 Jan 4;21(1):5.
doi: 10.1186/s12879-020-05672-6.

ODYSSEY clinical trial design: a randomised global study to evaluate the efficacy and safety of dolutegravir-based antiretroviral therapy in HIV-positive children, with nested

pharmacokinetic sub-studies to evaluate pragmatic WHO-weight-band based dolutegravir dosing

Cecilia L Moore[1], Anna Turkova[2], Hilda Mujuru[3], Adeodata Kekitiinwa[4], Abbas Lugemwa[5], Cissy M Kityo[6], Linda N Barlow-Mosha[7], Tim R Cressey[8 9 10], Avy Violari[11], Ebrahim Variava[12], Mark F Cotton[13], Moherndran Archary[14], Alexandra Compagnucci[15], Thanyawee Puthanakit[16], Osee Behuhuma[17], Yacine Saïdi[15], James Hakim[3], Pauline Amuge[4], Lorna Atwine[5], Victor Musiime[6], David M Burger[18], Clare Shakeshaft[2], Carlo Giaquinto[19], Pablo Rojo[20], Diana M Gibb[2], Deborah Ford[2], ODYSSEY Trial Team

Abstract

Background: Dolutegravir (DTG)-based antiretroviral therapy (ART) is highly effective and well-tolerated in adults and is rapidly being adopted globally. We describe the design of the ODYSSEY trial which evaluates the efficacy and safety of DTG-based ART compared with standard-of-care in children and adolescents. The ODYSSEY trial includes nested pharmacokinetic (PK) sub-studies which evaluated pragmatic World Health Organization (WHO) weight-band-based DTG dosing and opened recruitment to children < 14 kg while dosing was in development.

Methods: ODYSSEY (Once-daily DTG based ART in Young people vS. Standard thErapY) is an open-label, randomised, non-inferiority, basket trial comparing the efficacy and safety of DTG + 2 nucleos(t) ides (NRTIs) versus standard-of-care (SOC) in HIV-infected children < 18 years starting first-line ART (ODYSSEY A) or switching to second-line ART (ODYSSEY B). The primary endpoint is clinical or virological failure by 96 weeks.

Results: Between September 2016 and June 2018, 707 children weighing ≥14 kg were enrolled; including 311 ART-naïve children and 396 children starting second-line. 47% of children were enrolled in Uganda, 21% Zimbabwe, 20% South Africa, 9% Thailand, 4% Europe. 362 (51%) participants were male; median age [range] at enrolment was 12.2 years [2.9-18.0]. 82 (12%) children weighed 14 to < 20 kg, 135 (19%) 20 to < 25 kg, 206 (29%) 25 to < 35 kg, 284 (40%) ≥35 kg. 128 (18%) had WHO stage 3 and 60 (8%) WHO stage 4 disease. Challenges encountered include: (i) running the trial across high- to low-income countries with differing frequencies of standard-of-care viral load monitoring; (ii) evaluating pragmatic DTG dosing in PK sub-studies alongside FDA- and EMA-approved dosing and subsequently transitioning participants to new recommended doses; (iii) delays in dosing information for children weighing 3 to < 14 kg and rapid recruitment of ART-naïve older/heavier children, which led to capping recruitment of participants weighing ≥35 kg in ODYSSEY A and extending recruitment (above 700) to allow for ≥60 additional children weighing between 3 to < 14 kg with associated PK; (iv) a safety alert associated with DTG use during pregnancy, which required a review of the safety plan for adolescent girls.

Conclusions: By employing a basket design, to include ART-naïve and -experienced children, and nested PK sub-studies, the ODYSSEY trial efficiently evaluates multiple scientific questions regarding dosing and effectiveness of DTG-based ART in children.

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doi: 10.1016/S2352-3018(20)30189-2.

Simplified dolutegravir dosing for children with HIV weighing 20 kg or more: pharmacokinetic and safety substudies of the multicentre, randomised ODYSSEY trial

Pauline D J Bollen[1], Cecilia L Moore[2], Hilda A Mujuru[3], Shafic Makumbi[4], Adeodata R Kekitiinwa[5], Elisabeth Kaudha[6], Anna Parker[2], Godfrey Musoro[3], Annet Nanduudu[6], Abbas Lugemwa[4], Pauline Amuge[5], James G Hakim[3], Pablo Rojo[7], Carlo Giaquinto[8], Angela Colbers[9], Diana M Gibb[2], Deborah Ford[2], Anna Turkova[2], David M Burger[1], ODYSSEY trial team

Abstract

Background: Paediatric dolutegravir doses approved by stringent regulatory authorities (SRAs) for children weighing 20 kg to less than 40 kg until recently required 25 mg and 10 mg film-coated tablets. These tablets are not readily available in low-resource settings where the burden of HIV is highest. We did nested pharmacokinetic substudies in patients enrolled in the ODYSSEY-trial to evaluate simplified dosing in children with HIV.

Methods: We did pharmacokinetic and safety substudies within the open-label, multicentre, randomised ODYSSEY trial (NCT02259127) of children with HIV starting treatment in four research centres in Uganda and Zimbabwe. Eligible children were randomised to dolutegravir in ODYSSEY and weighed 20 kg to less than 40 kg. In children weighing 20 kg to less than 25 kg, we assessed dolutegravir's pharmacokinetics in children given once daily 25 mg film-coated tablets (approved by the SRAs at the time of the study) in part one of the study, and 50 mg film-coated tablets (adult dose) or 30 mg dispersible tablets in part two of the study. In children weighing 25 kg to less than 40 kg, we also assessed dolutegravir pharmacokinetics within-subject on film-coated tablet doses of 25 mg or 35 mg once daily, which were approved by the SRAs for the children's weight band; then switched to 50 mg film-coated tablets once daily. Steady-state 24 h dolutegravir plasma concentration-time pharmacokinetic profiling was done in all enrolled children at baseline and 1, 2, 3, 4, 6, and 24 h after observed dolutegravir intake. Target dolutegravir trough concentrations (C_{trough}) were based on reference adult pharmacokinetic data and safety was evaluated in all children in the corresponding weight bands who consented to pharmacokinetic studies and received the studied doses.

Findings: Between Sept 22, 2016, and May 31, 2018, we enrolled 62 black-African children aged from 6 years to younger than 18 years (84 pharmacokinetic-profiles). In children weighing 20 kg to less than 25 kg taking 25 mg film-coated tablets, the geometric mean (GM) C_{trough} (coefficient of variation) was 0·32 mg/L (94%), which was 61% lower than the GM C_{trough} of 0·83 mg/L (26%) in fasted adults on dolutegravir 50 mg once-daily; in children weighing 25 kg to less than 30 kg taking 25 mg film-coated tablets, the GM C_{trough} was 0·39 mg/L (48%), which was 54% lower than the GM C_{trough} in fasted adults; and in those 30 kg to less than 40 kg taking 35 mg film-coated tablets the GM C_{trough} was 0·46 mg/L (63%), which was 45% lower than the GM C_{trough} in fasted adults. On 50 mg film-coated tablets or 30 mg dispersible tablets, C_{trough} was close to the adult reference (with similar estimates on the two formulations in children in the 20 to <25 kg weight band), with total exposure (area under the concentration-time curve from 0 h to 24 h) in between reference values in adults dosed once and twice daily, where safety data are reassuring, although maximum concentrations were higher in children weighing 20 kg to less than 25 kg than in the twice-daily adult reference. Over a 24-week follow-up period in 47 children on 30 mg dispersible tablets or 50 mg film-coated tablets, none of the three reported adverse events (cryptococcal meningitis, asymptomatic anaemia, and asymptomatic neutropenia) were considered related to dolutegravir.

Interpretation: Adult dolutegravir 50 mg film-coated tablets given once daily provide appropriate pharmacokinetic profiles in children weighing 20 kg or more, with no safety

signal, allowing simplified practical dosing and rapid access to dolutegravir. These results informed the WHO 2019 dolutegravir paediatric dosing guidelines and have led to US Food and Drug Administration approval of adult dosing down to 20 kg.

HIV testing and systems of care

(See also: Vaccines – BCG vaccine and delayed administration in HIV exposed infants)

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doi: 10.1097/QAI.0000000000002383.

Impact of Routine Point-of-Care Versus Laboratory Testing for Early Infant Diagnosis of HIV: Results From a Multicountry Stepped-Wedge Cluster-Randomized Controlled Trial

Emma Sacks[1,2], Jennifer Cohn[3], Bernard Ochuka[4], Haurovi Mafaune[5], Addmore Chadambuka[5], Collins Odhiambo[4,6], Rose Masaba[4], George Githuka[7], Agnes Mahomva[8], Angela Mushavi[8], Jean-Francois Lemaire[3], Flavia Bianchi[2], Rhoderick Machekano[2]

Abstract

Background: Although the World Health Organization recommends HIV-exposed infants receive a 6-week diagnostic test, few receive results by 12 weeks. Point-of-care (POC) early infant diagnosis (EID) may improve timely diagnosis and treatment. This study assesses the impact of routine POC versus laboratory-based EID on return of results by 12 weeks of age.

Methods: This was a cluster-randomized stepped-wedge trial in Kenya and Zimbabwe. In each country, 18 health facilities were randomly selected for inclusion and randomized to timing of POC implementation.

Findings: Nine thousand five hundred thirty-nine infants received tests: 5115 laboratory-based and 4424 POC. In Kenya and Zimbabwe, respectively, caregivers were 1.29 times [95% confidence interval (CI): 1.27 to 1.30, P < 0.001] and 4.56 times (95% CI: 4.50 to 4.60, P < 0.001) more likely to receive EID results by 12 weeks of age with POC versus laboratory-based EID. POC significantly reduced the time between sample collection and return of results to caregiver by an average of 23.03 days (95% CI: 4.85 to 21.21, P < 0.001) in Kenya and 62.37 days (95% CI: 58.94 to 65.80, P < 0.001) in Zimbabwe. For HIV-infected infants, POC significantly increased the percentage initiated on treatment, from 43.2% to 79.6% in Zimbabwe, and resulted in a nonsignificant increase in Kenya from 91.7% to 100%. The introduction of POC EID also significantly reduced the time to antiretroviral therapy initiation by an average of 17.01 days (95% CI: 9.38 to 24.64, P < 0.001) in Kenya and 56.00 days (95% CI: 25.13 to 153.76, P < 0.001) in Zimbabwe.

Conclusions: POC confers significant advantage on the proportion of caregivers receiving timely EID results, and improves time to results receipt and treatment initiation for infected infants. Where laboratory-based EID systems are unable to deliver results to caregivers rapidly, POC should be implemented as part of an integrated testing system.

BMC Public Health. 2020 Dec 7;20(1):1879.
doi: 10.1186/s12889-020-09973-y.

Receipt of infant HIV DNA PCR test results is associated with a reduction in retention of HIV-exposed infants in integrated HIV care and healthcare services: a quantitative sub-study nested within a cluster randomised trial in rural Malawi

Elasma Milanzi[1,2], Victor Mwapasa[3], Jessica Joseph[4], Aurelie Jousset[5], Timothy Tchereni[5], Andrews Gunda[5], Jennipher Phiri[1], Jeanette C Reece[6,7]

Abstract

Background: Retention of HIV-infected mothers in integrated HIV and healthcare facilities is effective at reducing mother-to-child-transmission (MTCT) of HIV. In the context of Option B+, we examined maternal and HIV-exposed infant retention across three study arms to 18 months postpartum: mother-and-infant clinics (MIP), MIP with short-messaging service (MIP + SMS) and standard of care (SOC). In particular, we focused on the impact of mothers receiving an infant's HIV PCR test result on maternal and infant study retention.

Methods: A quantitative sub-study nested within a cluster randomised trial undertaken between May 2013 and August 2016 across 30 healthcare facilities in rural Malawi enrolling HIV-infected pregnant mothers and HIV-exposed infants on delivery, was performed. Survival probabilities of maternal and HIV-exposed infant study retention was estimated using Kaplan-Meier curves. Associations between mother's receiving an infant's HIV test result and in particular, an infant's HIV-positive result on maternal and infant study retention were modelled using time-varying multivariate Cox regression.

Results: Four hundred sixty-one, 493, and 396 HIV-infected women and 386, 399, and 300 HIV-exposed infants were enrolled across study arms; MIP, MIP + SMS and SOC, respectively. A total of 47.5% of mothers received their infant's HIV test results < 5 months postpartum. Receiving an infant's HIV result by mothers was associated with a 70% increase in infant non-retention in the study compared with not receiving an infant's result (HR = 1.70; P-value< 0.001). Receiving a HIV-positive result was associated with 3.12 times reduced infant retention compared with a HIV-negative result (P-value< 0.001). Of the infants with a HIV-negative test result, 87% were breastfed at their final study follow-up.

Conclusions: Receiving an infant's HIV test result was a driving factor for reduced infant study retention, especially an infant's HIV-positive test result. As most HIV-negative infants were still breastfed at their last follow-up, this indicates a large proportion of HIV-exposed infants were potentially at future risk of MTCT of HIV via breastfeeding but were unlikely to undergo follow-up HIV testing after breastfeeding cessation. Future studies to identify and address underlying factors associated with infant HIV testing and reduced infant retention could potentially improve infant retention in HIV/healthcare facilities.

BMJ Open. 2020 Nov 19;10(11):e043679.
doi: 10.1136/bmjopen-2020-043679.

Feasibility and acceptability of implementing early infant diagnosis of HIV in Papua New Guinea at the point of care: a qualitative exploration of health worker and key informant perspectives

Yasmin Mohamed[1,2], Martha Kupul[3], Janet Gare[3], Steven G Badman[4], Selina Silim[3], Andrew J Vallely[3,4], Stanley Luchters[5,2,6,7], Angela Kelly-Hanku[3,4], AAMI Study Group

Abstract

Introduction: Early infant diagnosis (EID) of HIV and timely initiation of antiretroviral therapy can significantly reduce morbidity and mortality among HIV-positive infants. Access to EID is limited in many low-income and middle-income settings, particularly those in which standard care involves dried blood spots (DBS) sent to centralised laboratories, such as in Papua New Guinea (PNG). We conducted a qualitative exploration of the feasibility and acceptability of implementing a point-of-care (POC) EID test (Xpert HIV-1 Qualitative assay) among health workers and key stakeholders working within the prevention of mother-to-child transmission of HIV (PMTCT) programme in PNG.
Methods: This qualitative substudy was conducted as part of a pragmatic trial to investigate the effectiveness of the Xpert HIV-1 Qualitative test for EID in PNG and Myanmar. Semistructured interviews were undertaken with 5 health workers and 13 key informants to explore current services, experiences of EID testing, perspectives on the Xpert test and the feasibility of integrating and scaling up POC EID in PNG. Coding was undertaken using inductive and deductive approaches, drawing on existing acceptability and feasibility frameworks.
Results: Health workers and key informants (N=18) felt EID at POC was feasible to implement and beneficial to HIV-exposed infants and their families, staff and the PMTCT programme more broadly. All study participants highlighted starting HIV-positive infants on treatment immediately as the main advantage of POC EID compared with standard care DBS testing. Health workers identified insufficient resources to follow up infants and caregivers and space constraints in hospitals as barriers to implementation. Participants emphasised the importance of adequate human resources, ongoing training and support, appropriate coordination and a sustainable supply of consumables to ensure effective scale-up of the test throughout PNG.
Conclusions: Implementation of POC EID in a low HIV prevalence setting such as PNG is likely to be both feasible and beneficial with careful planning and adequate resources.

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doi: 10.1371/journal.pone.0241245. eCollection 2020.

Caregiver experience and perceived acceptability of a novel near point-of-care early infant HIV diagnostic test among caregivers enrolled in the PMTCT program, Myanmar: A qualitative study

Win Lei Yee[1], Kyu Kyu Than[1], Yasmin Mohamed[2 3], Hla Htay[1], Htay Htay Tin[4], Win Thein[4], Latt Latt Kyaw[4], Win Win Yee[4], Moe Myat Aye[4], Steven G Badman[5], Andrew J Vallely[5 6], Stanley Luchters[2 3 7 8], Angela Kelly-Hanku[5 6], AAMI study group

Abstract
Background: The majority of HIV infection among children occurs through mother-to-child transmission. HIV exposed infants are recommended to have virological testing at birth or 4-6 weeks of age but challenges with centralized laboratory-based testing in Myanmar result in low testing rates and delays in result communication and treatment initiation. Decentralized point-of-care (POC) testing when integrated in prevention of mother-to-child transmission of HIV (PMTCT) services, can be an alternative to increase coverage of early infant diagnosis (EID) and timely engagement in HIV treatment and care.

Aim: This paper aims to explore experiences of caregivers of HIV-exposed infants enrolled in the PMTCT program in Myanmar and the perceived acceptability of point-of-care EID testing compared to conventional centralised laboratory-based testing.
Methods: This is a sub-study of the cluster randomised controlled stepped-wedge trial (Trial registration number: ACTRN12616000734460) that assessed the impact of near POC EID testing using Xpert HIV-1 Qual assay in four public hospitals in Myanmar. Caregivers of infants who were enrolled in the intervention phase of the main study, had been tested with both Xpert and standard of care tests and had received the results were eligible for this qualitative study. Semi-structured interviews were conducted with 23 caregivers. Interviews were audio recorded, transcribed verbatim and translated into English. Thematic data analysis was undertaken using NVivo 12 Software (QSR International).
Results: The majority of caregivers were satisfied with the quality of care provided by PMTCT services. However, they encountered social and financial access barriers to attend the PMTCT clinic regularly. Mothers had concerns about community stigma from the disclosure of their HIV status and the potential consequences for their infants. While medical care at the PMTCT clinics was free, caregivers sometimes experienced financial difficulties associated with out-of-pocket expenses for childbirth and transportation. Some caregivers had to choose not to attend work (impacting their income) or the adult antiretroviral clinic in order to attend the paediatric PMTCT clinic appointment. The acceptability of the Xpert testing process was high among the caregiver participants and more than half received the Xpert result on the same day as testing. Short turnaround time of the near POC EID testing enabled the caregivers to find out their infants' HIV status quicker, thereby shortening the stressful waiting time for results.
Conclusion: Our study identified important access challenges facing caregivers of HIV exposed infants and high acceptability of near POC EID testing. Improving the retention rate in the PMTCT and EID programs necessitates careful attention of program managers and policy makers to these challenges, and POC EID represents a potential solution.

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Financial incentives to increase pediatric HIV testing: a randomized trial

Irene N Njuguna[1 2 3], Anjuli D Wagner[2], Jillian Neary[1], Vincent O Omondi[4], Verlinda A Otieno[4], Anita Orimba[4], Cyrus Mugo[2 3], Joseph B Babigumira[2 5], Carol Levin[2], Barbra A Richardson[2 6], Elizabeth Maleche-Obimbo[7], Dalton C Wamalwa[7], Grace John-Stewart[1 2 8 9], Jennifer Slyker[1 2]

Abstract
Background: Financial incentives can motivate desirable health behaviors, including adult HIV testing. Data regarding the effectiveness of financial incentives for HIV testing in children, who require urgent testing to prevent mortality, are lacking.
Methods: In a five-arm unblinded randomized controlled trial, adults living with HIV attending 19 HIV clinics in Western Kenya, with children 0-12 years of unknown HIV status, were randomized with equal allocation to $0, $1.25, $2.50, $5 or $10. Payment was conditional on child HIV testing within 2 months. Block randomization with fixed block sizes was used; participants and study staff were unblinded at randomization. Primary analysis

was intent-to-treat, with predefined primary outcomes of completing child HIV testing and time to testing.
Results: Of 452 caregivers, 90, 89, 93, 92 and 88 were randomized to $0, $1.25, $2.50, $5.00, and $10.00, respectively. Of those, 31 (34%), 31 (35%), 44 (47%), 51 (55%), and 54 (61%) in the $0, $1.25, $2.50, $5.00, and $10.00 arms, respectively, completed child testing. Compared with the $0 arm, and adjusted for site, caregivers in the $10.00 arm had significantly higher uptake of testing [relative risk: 1.80 (95% CI 1.15--2.80), P = 0.010]. Compared with the $0 arm, and adjusted for site, time to testing was significantly faster in the $5.00 and $10.00 arms [hazard ratio: 1.95 (95% CI 1.24--3.07) P = 0.004, 2.42 (95% CI 1.55--3.79), P < 0.001, respectively).
Conclusion: Financial incentives are effective in improving pediatric HIV testing among caregivers living with HIV.

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A Continuous Quality Improvement Intervention to Improve Antenatal HIV Care Testing in Rural South Africa: Evaluation of Implementation in a Real-World Setting

H Manisha Yapa[1,2], Wendy Dhlomo-Mphatswe[3], Mosa Moshabela[2,4], Jan-Walter De Neve[5], Carina Herbst[2], Awachana Jiamsakul[1], Kathy Petoumenos[1], Frank A Post[6], Deenan Pillay[2,7], Till Bärnighausen[2,5,8,9], Sally Wyke[2,10]

Abstract
Background: We evaluated continuous quality improvement (CQI) targeting antenatal HIV care quality in rural South Africa using a stepped-wedge cluster-randomised controlled trial (Management and Optimisation of Nutrition, Antenatal, Reproductive, Child health, MONARCH) and an embedded process evaluation. Here, we present results of the process evaluation examining determinants of CQI practice and 'normalisation.'
Methods: A team of CQI mentors supported public-sector health workers in seven primary care clinics to (1) identify root causes of poor HIV viral load (VL) monitoring among pregnant women living with HIV and repeat HIV testing among pregnant women not living with HIV, and (2) design and iteratively test their own solutions. We used a mixed methods evaluation with *field notes* from CQI mentors ('dose' and 'reach' of CQI, causes of poor HIV care testing rates, implemented change ideas); *patient medical records* (HIV care testing by clinic and time step); and *semi-structured interviews* with available health workers. We analysed field notes andsemi-structured *interviews* for determinants of CQI implementation and 'normalisation' using Normalisation Process Theory (NPT) and Tailored Implementation of Chronic Diseases (TICD) frameworks.
Results: All interviewed health workers found the CQI mentors and methodology helpful for quality improvement. Total administered 'dose' was higher than planned but 'reach' was limited by resource constraints, particularly staffing shortages. Simple workable improvements to identified root causes were implemented, such as a patient tracking notebook and results filing system. VL monitoring improved over time, but not repeat HIV testing. Besides resource constraints, gaps in knowledge of guidelines, lack of leadership, poor clinical documentation, and data quality gaps reduced CQI implementation fidelity and normalisation.

Conclusion: While CQI holds promise, we identified several health system challenges. Priorities for policy makers include improving staffing and strategies to improve clinical documentation. Additional support with implementing clinical guidelines and improving routine data quality are needed. Normalising CQI may be challenging without concurrent health system improvements.

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A mobile health-facilitated behavioural intervention for community health workers improves exclusive breastfeeding and early infant HIV diagnosis in India: a cluster randomized trial

Nishi Suryavanshi[1], Abhay Kadam[1], Nikhil Gupte[2], Asha Hegde[3], Savita Kanade[1], Srilatha Sivalenka[4], V Sampath Kumar[4], Amita Gupta[2], Robert C Bollinger[2], Anita Shankar[5], Jane McKenzie-White[2], Vidya Mave[2]

Abstract

Introduction: India's national AIDS Control Organization implemented World Health Organization's option B+ HIV prevention of mother-to-child transmission (PMTCT) guidelines in 2013. However, scalable strategies to improve uptake of new PMTCT guidelines to reduce new infection rates are needed. This study assessed impact of Mobile Health-Facilitated Behavioral Intervention on the uptake of PMTCT services.

Methods: A cluster-randomized trial of a mobile health (mHealth)-supported behavioural training intervention targeting outreach workers (ORWs) was conducted in four districts of Maharashtra, India. Clusters (one Integrated Counselling and Testing Center (ICTC, n = 119), all affiliated ORWs (n = 116) and their assigned HIV-positive pregnant/postpartum clients (n = 1191)) were randomized to standard-of-care (SOC) ORW training vs. the COMmunity home Based INDia (COMBIND) intervention - specialized behavioural training plus a tablet-based mHealth application to support ORW-patient communication and patient engagement in HIV care. Impact on uptake of maternal antiretroviral therapy at delivery, exclusive breastfeeding at six months, infant nevirapine prophylaxis, and early infant diagnosis at six months was assessed using multi-level random-effects logistic regression models.

Results: Of 1191 HIV-positive pregnant/postpartum women, 884 were eligible for primary outcome assessment; 487 were randomized to COMBIND. Multivariable analyses identified no statistically significant differences in any primary outcome by study arm. COMBIND was associated with higher uptake of exclusive breastfeeding at two months (adjusted Odds Ratio (aOR), 2.10; 95% CI 1.06 to 4.15) and early infant diagnosis at six weeks (aOR, 2.19; 95% CI 1.05 to 3.98) than SOC.

Conclusions: The COMBIND intervention was easily integrated into India's existing PMTCT programme and improved early uptake of two PMTCT components that require self-motivated health-seeking behaviour, thus providing preliminary evidence to support COMBIND as a potentially scalable PMTCT strategy. Further study would identify modifications needed to optimize other PMTCT outcomes.

Cotrimoxazole preventative therapy

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Brief Report: Cessation of Long-Term Cotrimoxazole Prophylaxis in HIV-Infected Children Does Not Alter the Carriage of Antimicrobial Resistance Genes

Freddy Francis[1], Ethan K Gough[2], Thaddeus J Edens[3], Chipo Berejena[4], Mutsawashe Bwakura-Dangarembizi[4], Annie Shonhai[4], Kusum J Nathoo[4], Magdalena Glass[5], Diana M Gibb[6], Andrew J Prendergast[7,8], Amee R Manges[5,9]

Abstract

Background: Cotrimoxazole (CTX) is a broad-spectrum antimicrobial, combining trimethoprim and sulfamethoxazole. CTX prophylaxis reduces mortality and morbidity among people living with HIV in regions with high prevalence of bacterial infections and malaria. The Antiretroviral research for Watoto trial evaluated the effect of stopping versus continuing CTX prophylaxis in sub-Saharan Africa.

Methods: In this study, 72 HIV-infected Zimbabwean children, on antiretroviral therapy, provided fecal samples at 84 and 96 weeks after randomization to continue or stop CTX. DNA was extracted for whole metagenome shotgun sequencing, with sequencing reads mapped to the Comprehensive Antibiotic Resistance Database to identify CTX and other antimicrobial resistance genes.

Results: There were minimal differences in the carriage of CTX resistance genes between groups. The dfrA1 gene, conferring trimethoprim resistance, was significantly higher in the continue group (P = 0.039) and the tetA(P) gene conferring resistance to tetracycline was significantly higher in the stop group (P = 0.013). CTX prophylaxis has a role in shaping the resistome; however, stopping prophylaxis does not decrease resistance gene abundance.

Conclusions: No differences were observed in resistance gene carriage between the stop and continue groups. The previously shown multi-faceted protective effects of CTX in antiretroviral research for Watoto trial clinical outcomes are not outweighed by the risk of multi-drug resistance gene selection due to prophylaxis. These findings are reassuring, given current recommendations for long-term CTX prophylaxis among children living with HIV in sub-Saharan Africa to decrease mortality and morbidity.

Management of HIV-related conditions

Dev Med Child Neurol. 2020 Nov;62(11):1309-1316.
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Recovery of HIV encephalopathy in perinatally infected children on antiretroviral therapy

Steve Innes[1,2], Barbara Laughton[1,2], Ronald van Toorn[2], Kennedy Otwombe[3,4], Afaaf Liberty[3,4], Els Dobbels[1], Avy Violari[3,4], Mariana Kruger[2], Mark F Cotton[1,2]

Abstract

Aim: To describe the trajectory of clinical signs in children who developed human immunodeficiency virus encephalopathy (HIVE) after starting early antiretroviral therapy (ART).

Method: This was a retrospective case-cohort description of HIVE among Cape Town participants from the Children with HIV Early AntiRetroviral treatment (CHER) trial. Criteria for HIVE diagnosis were at least two of: (1) acquired central motor deficit, (2) impaired brain growth, and (3) failure to attain or loss of developmental milestones in the absence of an alternative aetiology.
Results: Of 133 surviving participants who initiated ART at a median age of 9 weeks and who were followed until a median age of 6 years, 20 (12%) developed HIVE at a median age 31 months (interquartile range 19-37). In these, the first neurological deterioration was noticed at a median age of 19 months, when 16 were on ART and nine had undetectable HIV viral load for a median of 12 months. Signs of upper motor neurons were present in 18, of whom 12 resolved and four had persistent spastic diplegia; 19 had motor delay, of whom 14 resolved; 12 had language delay, of whom 11 resolved; and 16 had impaired brain growth, of whom only five recovered. For the 16 participants already on ART at HIVE diagnosis, regimens were not altered in response to diagnosis.
Interpretation: HIVE may occur despite early ART initiation and virological suppression and then resolve on unchanged ART, most likely as intrathecal inflammation subsides.
What this paper adds: Despite suppressive antiretroviral therapy, children can develop human immunodeficiency virus encephalopathy, The most common manifestations are motor deficits and impaired brain growth. Most experience improvement, with many resolving without additional intervention.

JAMA Netw Open. 2020 Dec 1;3(12):e2028484.
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Effect of Once-Weekly Azithromycin vs Placebo in Children With HIV-Associated Chronic Lung Disease: The BREATHE Randomized Clinical Trial

Rashida A Ferrand[1,2], Grace McHugh[2], Andrea M Rehman[3], Hilda Mujuru[4], Victoria Simms[2,3], Edith D Majonga[2], Mark P Nicol[5,6], Trond Flaegstad[7,8], Tore J Gutteberg[7,9], Carmen Gonzalez-Martinez[10,11], Elizabeth L Corbett[1,10], Sarah L Rowland-Jones[12], Katharina Kranzer[1,2], Helen A Weiss[3], Jon O Odland[7,13], BREATHE Trial Group

Abstract

Importance: HIV-associated chronic lung disease (HCLD) in children is associated with small airways disease, is common despite antiretroviral therapy (ART), and is associated with substantial morbidity. Azithromycin has antibiotic and immunomodulatory activity and may be effective in treating HCLD through reducing respiratory tract infections and inflammation.
Objective: To determine whether prophylactic azithromycin is effective in preventing worsening of lung function and in reducing acute respiratory exacerbations (AREs) in children with HCLD taking ART.
Design, setting, and participants: This double-blind, placebo-controlled, randomized clinical trial (BREATHE) was conducted between 2016 and 2019, including 12 months of follow-up, at outpatient HIV clinics in 2 public sector hospitals in Malawi and Zimbabwe. Participants were randomized 1:1 to intervention or placebo, and participants and study personnel were blinded to treatment allocation. Participants included children aged 6 to 19 years with perinatally acquired HIV and HCLD (defined as forced expiratory volume in 1 second [FEV1] z score < -1) who were taking ART for 6 months or longer. Data analysis was performed from September 2019 to April 2020.

Intervention: Once-weekly oral azithromycin with weight-based dosing, for 48 weeks.
Main outcomes and measures: All outcomes were prespecified. The primary outcome was the mean difference in FEV1 z score using intention-to-treat analysis for participants seen at end line. Secondary outcomes included AREs, all-cause hospitalizations, mortality, and weight-for-age z score.
Results: A total of 347 individuals (median [interquartile range] age, 15.3 [12.7-17.7] years; 177 boys [51.0%]) were randomized, 174 to the azithromycin group and 173 to the placebo group; 162 participants in the azithromycin group and 146 placebo group participants had a primary outcome available and were analyzed. The mean difference in FEV1 z score was 0.06 (95% CI, -0.10 to 0.21; P = .48) higher in the azithromycin group than in the placebo group, a nonsignificant difference. The rate of AREs was 12.1 events per 100 person-years in the azithromycin group and 24.7 events per 100 person-years in the placebo groups (hazard ratio, 0.50; 95% CI, 0.27 to 0.93; P = .03). The hospitalization rate was 1.3 events per 100 person-years in the azithromycin group and 7.1 events per 100 person-years in the placebo groups, but the difference was not significant (hazard ratio, 0.24; 95% CI, 0.06 to 1.07; P = .06). Three deaths occurred, all in the placebo group. The mean weight-for-age z score was 0.03 (95% CI, -0.08 to 0.14; P = .56) higher in the azithromycin group than in the placebo group, although the difference was not significant. There were no drug-related severe adverse events.
Conclusions and relevance: In this randomized clinical trial specifically addressing childhood HCLD, once-weekly azithromycin did not improve lung function or growth but was associated with reduced AREs; the number of hospitalizations was also lower in the azithromycin group but the difference was not significant. Future research should identify patient groups who would benefit most from this intervention and optimum treatment length, to maximize benefits while reducing the risk of antimicrobial resistance.

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doi: 10.1186/s12903-021-01441-2.

Dental caries in association with viral load in children living with HIV in Phnom Penh, Cambodia: a cross-sectional study

Kimiyo Kikuchi[1], Junko Yasuoka[2], Sovannary Tuot[3 4], Sumiyo Okawa[5], Sokunthea Yem[3], Pheak Chhoun[3], Makoto Murayama[6], Chantheany Huot[7], Siyan Yi[3 8 9 10]

Abstract
Background: Oral health status is associated with the overall health among people living with human immunodeficiency virus (HIV) infection. However, it is unclear whether dental caries is associated with the viral load in this population. Particularly, dental caries among children living with HIV needs better understanding as this can affect their overall health and future well-being. This study assessed the association between dental caries and viral load among children living with HIV in Phnom Penh, Cambodia.
Methods: This cross-sectional study, conducted at the National Pediatric Hospital as a baseline survey of a randomized controlled trial, included 328, 3-15-year-old children living with HIV and their primary caregivers. Calibrated and trained examiners conducted oral examinations for dental caries (DMFT/dmft index) in the children and retrieved the latest HIV viral load data from the hospital's patient information system. On the dental examination day, the children and their caregivers were invited to answer a questionnaire-based

interview. Multiple logistic regression analysis was conducted to assess the association between dental caries and viral load. The cut-off point for undetectable viral load was set at < 40 copies/mL.
Results: Data from 328 children were included in the analysis; 68.3% had an undetectable viral load. The mean DMFT/dmft was 7.7 (standard deviation = 5.0). Adjusted regression analysis showed that dental caries in permanent or deciduous teeth was positively associated with detectable viral load (adjusted odds ratio [AOR]: 1.07, 95% confidence interval [CI]: 1.01-1.14). Conversely, antiretroviral therapy of ≥ 1 year and self-reported better adherence to antiretroviral drugs were negatively associated with detectable viral load. Among children with detectable viral load, dental caries in permanent or deciduous teeth was positively associated with non-suppression of viral load (> 1000 copies/mL) (AOR: 1.12, CI: 1.03-1.23).
Conclusions: Dental caries was associated with viral load status detection among children living with HIV. This finding suggests that dental caries may affect their immune status. The oral health of children living with HIV should be strengthened, and further research is needed to clarify the causal relationship between viral load and oral health status.

Vaccines in HIV-infected children

Nutrition, growth and development of children with HIV

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doi: 10.1038/s41598-020-68143-7.
Plasma proteomics reveals markers of metabolic stress in HIV infected children with severe acute malnutrition
Gerard Bryan Gonzales[1,2], James M Njunge[3,4], Bonface M Gichuki[3,4], Bijun Wen[5,6], Isabel Potani[3], Wieger Voskuijl[3,7,8], Robert H J Bandsma[3,5,6], James A Berkley[3,4,9]
Abstract
HIV infection affects up to 30% of children presenting with severe acute malnutrition (SAM) in Africa and is associated with increased mortality. Children with SAM are treated similarly regardless of HIV status, although mechanisms of nutritional recovery in HIV and/or SAM are not well understood. We performed a secondary analysis of a clinical trial and plasma proteomics data among children with complicated SAM in Kenya and Malawi. Compared to children with SAM without HIV (n = 113), HIV-infected children (n = 54) had evidence (false discovery rate (FDR) corrected p < 0.05) of metabolic stress, including enriched pathways related to inflammation and lipid metabolism. Moreover, we observed reduced plasma levels of zinc-α-2-glycoprotein, butyrylcholinesterase, and increased levels of complement C2 resembling findings in metabolic syndrome, diabetes and other non-communicable diseases. HIV was also associated (FDR corrected p < 0.05) with higher plasma levels of inflammatory chemokines. Considering evidence of biomarkers of metabolic stress, it is of potential concern that our current treatment strategy for SAM regardless of HIV status involves a high-fat therapeutic diet. The results of this study suggest a need for clinical trials of therapeutic foods that meet the specific metabolic needs of children with HIV and SAM.

Prevention of mother to child transmission of HIV and maternal HIV care

AIDS Behav. 2021 Mar;25(3):992-1000.
doi: 10.1007/s10461-020-03060-4. Epub 2020 Oct 8.

Effect of Enhanced Adherence Package on Early ART Uptake Among HIV-Positive Pregnant Women in Zambia: An Individual Randomized Controlled Trial

Mwangelwa Mubiana-Mbewe[1], Samuel Bosomprah[2,3], Jillian L Kadota[2,4], Aybüke Koyuncu[2], Thankian Kusanathan[5], Keith Mweebo[6], Kebby Musokotwane[6], Priscilla L Mulenga[7], Benjamin H Chi[8], Michael J Vinikoor[2,9]

Abstract

We evaluated the effect of an option B-plus Enhanced Adherence Package (BEAP), on early ART uptake in a randomized controlled trial. HIV-positive, ART naïve pregnant women in Lusaka, Zambia, were randomized to receive BEAP (phone calls/home visits, additional counseling, male partner engagement and missed-visit follow-up) versus standard of care (SOC). The primary outcome was initiating and remaining on ART at 30 days. Analysis was by intention to treat (ITT) using logistic regression. Additional per protocol analysis was done. We enrolled 454 women; 229 randomized to BEAP and 225 to SOC. Within 30 days of eligibility, 445 (98.2%) initiated ART. In ITT analysis, 82.5% BEAP versus 80.4% SOC participants reached primary outcome (crude relative risk [RR] 1.03; 95% confidence interval [CI] 0.91-1.16; Wald test statistic = 0.44; p-value = 0.66). In per protocol analysis, (92 participants (40.2%) excluded), 91.9% BEAP versus 80.4% SOC participants reached primary outcome (crude RR 1.14; 95% CI 1.02-1.29; Wald test statistic = 2.23; p-value = 0.03). Early ART initiation in pregnancy was nearly universal but there was early drop out suggesting need for additional adherence support

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Population-level viral suppression among pregnant and postpartum women in a universal test and treat trial

Jane Kabami[1,2], Laura B Balzer[3], Hachem Saddiki[3], James Ayieko[4], Dalsone Kwarisiima[2], Mucunguzi Atukunda[2], Edwin D Charlebois[5], Tamara D Clark[5], Catherine A Koss[5], Theodore Ruel[5], Elizabeth A Bukusi[4], Craig R Cohen[5], Phillipa Musoke[1], Maya L Petersen[6], Diane V Havlir[5], Moses R Kamya[1,2], Gabriel Chamie[5]

Abstract

Objective(s): We sought to determine whether universal 'test and treat' (UTT) can achieve gains in viral suppression beyond universal antiretroviral treatment (ART) eligibility during pregnancy and postpartum, among women living with HIV.

Design: A community cluster randomized trial.

Methods: The SEARCH UTT trial compared an intervention of annual population testing and universal ART with a control of baseline population testing with ART by country standard,

including ART eligibility for all pregnant/postpartum women, in 32 communities in Kenya and Uganda. When testing, women were asked about current pregnancy and live births over the prior year and, if HIV-infected, had their viral load measured. Between arms, we compared population-level viral suppression (HIV RNA <500 copies/ml) among all pregnant/postpartum HIV-infected women at study close (year 3). We also compared year-3 population-level viral suppression and predictors of viral suppression among all 15 to 45-year-old women by arm.
Results: At baseline, 92 and 93% of 15 to 45-year-old women tested for HIV: HIV prevalence was 12.6 and 12.3%, in intervention and control communities, respectively. Among HIV-infected women self-reporting pregnancy/live birth, prevalence of viral suppression was 42 and 44% at baseline, and 81 and 76% (P = 0.02) at year 3, respectively. Among all 15 to 45-year-old HIV-infected women, year-3 population-level viral suppression was higher in intervention (77%) versus control (68%; P < 0.001). Pregnancy/live birth was a predictor of year-3 viral suppression in control (P = 0.016) but not intervention (P = 0.43). Younger age was a risk factor for nonsuppression in both arms.
Conclusion: The SEARCH intervention resulted in higher population viral suppression among pregnant/postpartum women than a control of baseline universal testing with ART eligibility for pregnant/postpartum women.

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doi: 10.1371/journal.pmed.1003150. eCollection 2020 Oct.

The impact of continuous quality improvement on coverage of antenatal HIV care tests in rural South Africa: Results of a stepped-wedge cluster-randomised controlled implementation trial

H Manisha Yapa[1,2], Jan-Walter De Neve[3], Terusha Chetty[4], Carina Herbst[2], Frank A Post[5], Awachana Jiamsakul[1], Pascal Geldsetzer[3,6], Guy Harling[2,7], Wendy Dhlomo-Mphatswe[8], Mosa Moshabela[2,9], Philippa Matthews[2,10], Osondu Ogbuoji[11], Frank Tanser[2,9,12,13], Dickman Gareta[2], Kobus Herbst[2], Deenan Pillay[2,14], Sally Wyke[2,15], Till Bärnighausen[2,3,7,16,17]

Abstract
Background: Evidence for the effectiveness of continuous quality improvement (CQI) in resource-poor settings is very limited. We aimed to establish the effects of CQI on quality of antenatal HIV care in primary care clinics in rural South Africa.
Methods and findings: We conducted a stepped-wedge cluster-randomised controlled trial (RCT) comparing CQI to usual standard of antenatal care (ANC) in 7 nurse-led, public-sector primary care clinics-combined into 6 clusters-over 8 steps and 19 months. Clusters randomly switched from comparator to intervention on pre-specified dates until all had rolled over to the CQI intervention. Investigators and clusters were blinded to randomisation until 2 weeks prior to each step. The intervention was delivered by trained CQI mentors and included standard CQI tools (process maps, fishbone diagrams, run charts, Plan-Do-Study-Act [PDSA] cycles, and action learning sessions). CQI mentors worked with health workers, including nurses and HIV lay counsellors. The mentors used the standard CQI tools flexibly, tailored to local clinic needs. Health workers were the direct recipients of the intervention, whereas the ultimate beneficiaries were pregnant women attending ANC. Our 2 registered primary

endpoints were viral load (VL) monitoring (which is critical for elimination of mother-to-child transmission of HIV [eMTCT] and the health of pregnant women living with HIV) and repeat HIV testing (which is necessary to identify and treat women who seroconvert during pregnancy). All pregnant women who attended their first antenatal visit at one of the 7 study clinics and were ≥18 years old at delivery were eligible for endpoint assessment. We performed intention-to-treat (ITT) analyses using modified Poisson generalised linear mixed effects models. We estimated effect sizes with time-step fixed effects and clinic random effects (Model 1). In separate models, we added a nested random clinic-time step interaction term (Model 2) or individual random effects (Model 3). Between 15 July 2015 and 30 January 2017, 2,160 participants with 13,212 ANC visits (intervention n = 6,877, control n = 6,335) were eligible for ITT analysis. No adverse events were reported. Median age at first booking was 25 years (interquartile range [IQR] 21 to 30), and median parity was 1 (IQR 0 to 2). HIV prevalence was 47% (95% CI 42% to 53%). In Model 1, CQI significantly increased VL monitoring (relative risk [RR] 1.38, 95% CI 1.21 to 1.57, p < 0.001) but did not improve repeat HIV testing (RR 1.00, 95% CI 0.88 to 1.13, p = 0.958). These results remained essentially the same in both Model 2 and Model 3. Limitations of our study include that we did not establish impact beyond the duration of the relatively short study period of 19 months, and that transition steps may have been too short to achieve the full potential impact of the CQI intervention.
Conclusions: We found that CQI can be effective at increasing quality of primary care in rural Africa. Policy makers should consider CQI as a routine intervention to boost quality of primary care in rural African communities. Implementation research should accompany future CQI use to elucidate mechanisms of action and to identify factors supporting long-term success.

HIV vaccine

(see Vaccine – HIV vaccine)

Helminths

(See also Anaemia, Diarrhoea, Micronutrients and food fortification, Malaria and HIV)

PLoS Negl Trop Dis. 2021 May 12;15(5):e0009292.
doi: 10.1371/journal.pntd.0009292. Online ahead of print.
Epidemiology of soil-transmitted helminths following sustained implementation of routine preventive chemotherapy: Demographics and baseline results of a cluster randomised trial in southern Malawi
Stefan Witek-McManus[1], James Simwanza[2], Alvin B Chisambi[2], Stella Kepha[1 3 4], Zachariah Kamwendo[2], Alfred Mbwinja[5], Lyson Samikwa[5], William E Oswald[1], David S Kennedy[1], Joseph W S Timothy[1], Hugo Legge[1], Sean R Galagan[6], Mira Emmanuel-Fabula[6], Fabian Schaer[7], Kristjana Ásbjörnsdóttir[8], Katherine E Halliday[1], Judd L Walson[6 8 9], Lazarus Juziwelo[10], Robin L Bailey[11], Khumbo Kalua[2 5], Rachel L Pullan[1]
Abstract

Malawi has successfully leveraged multiple delivery platforms to scale-up and sustain the implementation of preventive chemotherapy (PCT) for the control of morbidity caused by soil-transmitted helminths (STH). Sentinel monitoring demonstrates this strategy has been successful in reducing STH infection in school-age children, although our understanding of the contemporary epidemiological profile of STH across the broader community remains limited. As part of a multi-site trial evaluating the feasibility of interrupting STH transmission across three countries, this study aimed to describe the baseline demographics and the prevalence, intensity and associated risk factors of STH infection in Mangochi district, southern Malawi. Between October-December 2017, a community census was conducted across the catchment area of seven primary healthcare facilities, enumerating 131,074 individuals across 124 villages. A cross-sectional parasitological survey was then conducted between March-May 2018 in the censused area as a baseline for a cluster randomised trial. An age-stratified random sample of 6,102 individuals were assessed for helminthiasis by Kato-Katz and completed a detailed risk-factor questionnaire. The age-cluster weighted prevalence of any STH infection was 7.8% (95% C.I. 7.0%-8.6%) comprised predominantly of hookworm species and of entirely low-intensity infections. The presence and intensity of infection was significantly higher in men and in adults. Infection was negatively associated with risk factors that included increasing levels of relative household wealth, higher education levels of any adult household member, current school attendance, or recent deworming. In this setting of relatively high coverage of sanitation facilities, there was no association between hookworm and reported access to sanitation, handwashing facilities, or water facilities. These results describe a setting that has reduced the prevalence of STH to a very low level and confirms many previously recognised risk-factors for infection. Expanding the delivery of anthelmintics to groups where STH infection persist could enable Malawi to move past the objective of elimination of morbidity, and towards the elimination of STH.

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Epidemiology of soil transmitted helminths and risk analysis of hookworm infections in the community: Results from the DeWorm3 Trial in southern India

Sitara S R Ajjampur[1], Saravanakumar Puthupalayam Kaliappan[1], Katherine E Halliday[2 3], Gokila Palanisamy[1], Jasmine Farzana[1], Malathi Manuel[1], Dilip Abraham[1], Selvi Laxmanan[1], Kumudha Aruldas[1], Anuradha Rose[4], David S Kennedy[2], William E Oswald[2], Rachel L Pullan[2], Sean R Galagan[3 5], Kristjana Ásbjörnsdóttir[3 6], Roy M Anderson[7], Jayaprakash Muliyil[1], Rajiv Sarkar[8], Gagandeep Kang[1], Judd L Walson[3 5 9]

Abstract

Since 2015, India has coordinated the largest school-based deworming program globally, targeting soil-transmitted helminths (STH) in ~250 million children aged 1 to 19 years twice yearly. Despite substantial progress in reduction of morbidity associated with STH, reinfection rates in endemic communities remain high. We conducted a community based parasitological survey in Tamil Nadu as part of the DeWorm3 Project-a cluster-randomised trial evaluating the feasibility of interrupting STH transmission at three geographically distinct sites in Africa and Asia-allowing the estimation of STH prevalence and analysis of associated factors. In India, following a comprehensive census, enumerating 140,932 individuals in 36,536 households along with geospatial mapping of households, an age-stratified sample of individuals was recruited into a longitudinal monitoring cohort

(December 2017-February 2018) to be followed for five years. At enrolment, a total of 6089 consenting individuals across 40 study clusters provided a single adequate stool sample for analysis using the Kato-Katz method, as well as answering a questionnaire covering individual and household level factors. The unweighted STH prevalence was 17.0% (95% confidence interval [95%CI]: 16.0-17.9%), increasing to 21.4% when weighted by age and cluster size. Hookworm was the predominant species, with a weighted infection prevalence of 21.0%, the majority of which (92.9%) were light intensity infections. Factors associated with hookworm infection were modelled using mixed-effects multilevel logistic regression for presence of infection and mixed-effects negative binomial regression for intensity. The prevalence of both Ascaris lumbricoides and Trichuris trichiura infections were rare (<1%) and risk factors were therefore not assessed. Increasing age (multivariable odds ratio [mOR] 21.4, 95%CI: 12.3-37.2, p<0.001 for adult age-groups versus pre-school children) and higher vegetation were associated with an increased odds of hookworm infection, whereas recent deworming (mOR 0.3, 95%CI: 0.2-0.5, p<0.001) and belonging to households with higher socioeconomic status (mOR 0.3, 95%CI: 0.2-0.5, p<0.001) and higher education level of the household head (mOR 0.4, 95%CI: 0.3-0.6, p<0.001) were associated with lower odds of hookworm infection in the multilevel model. The same factors were associated with intensity of infection, with the use of improved sanitation facilities also correlated to lower infection intensities (multivariable infection intensity ratio [mIIR] 0.6, 95%CI: 0.4-0.9, p<0.016). Our findings suggest that a community-based approach is required to address the high hookworm burden in adults in this setting. Socioeconomic, education and sanitation improvements alongside mass drug administration would likely accelerate the drive to elimination in these communities.

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Hand hygiene intervention to optimise soil-transmitted helminth infection control among primary school children: the Mikono Safi cluster randomised controlled trial in northwestern Tanzania

Kenneth Makata[1], Jeroen Ensink[2], Philip Ayieko[1 2 3], Christian Hansen[1 2], Simon Sichalwe[1], Julius Mngara[3], Onike Mcharo[1], Humphrey Mazigo[4], Jeremiah Seni[5], Robert Dreibelbis[2], Sarah Rockowitz[6], Elialilia Okello[1], Heiner Grosskurth[1 2 3], Safari Kinung'hi[3], Saidi Kapiga[7 8 9]

Abstract

Background: Soil-transmitted helminth (STH) infections are highly prevalent in resource-limited countries. We assessed the effect of a combination intervention aiming to enhance handwashing with soap on STH reinfection following mass drug administration among primary school children in Kagera region, Northwestern Tanzania.

Methods: We conducted a cluster randomised trial in sixteen primary schools with known high STH prevalence. Schools were randomly assigned in a 1:1 ratio to either receive the intervention or continue with routine health education. The intervention included teacher-led classroom teaching, parental engagement sessions, environmental modifications and improved handwashing stations. The evaluation involved two cross-sectional surveys in a representative sample of students, with the end-line survey conducted 12 months after the baseline survey. The primary outcome was the combined prevalence of Ascaris lumbricoides

and Trichuris trichiura infections at the end-line survey. Secondary outcomes included reported handwashing behaviour, the prevalence and intensity of individual STHs, and hand contamination with STH ova and coliform bacteria. End-line STH prevalence and intensity were adjusted for baseline differences of potential confounders.
Results: At the end-line survey, 3081 school children (1566 from intervention schools and 1515 from control schools) provided interview data and stool specimens. More school children in the intervention group reported the use of water and soap during handwashing compared to school children in the control group (58% vs. 35%; aOR=1.76, 95%CI 1.28-2.43, p=0.001). The combined prevalence of A. lumbricoides and T. trichiura infections was 39% in both trial arms (aOR = 1.19; 95%CI 0.74-1.91). The prevalence of A. lumbricoides was 15% in the intervention and 17% in the control arm (aOR =1.24, 95%CI 0.59-2.59) and that of T. trichiura was 31% in both arms (aOR=1.17, 95%CI 0.73-1.88). No significant differences were found for STH infection intensity in both the main study and the hand contamination sub-study.
Conclusions: The intervention was effective in increasing reported handwashing behaviour at school, but failed to show a similar effect in the home. The intervention had no effect on STH infection, possibly due to infection in the home environment, other transmission routes such as contaminated water or food or limited changes in school children's handwashing behaviour.

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Anthelminthic treatment receipt and its predictors in Lake Victoria fishing communities, Uganda: Intervention coverage results from the LaVIISWA cluster randomised trial

Hellen Akurut[1], Richard E Sanya[1,2], Lawrence Lubyayi[1], Margaret Nampijja[1], Moses Kizza[1], James Kaweesa[3], Robert Kizindo[1], Moses Sewankambo[1], Denis Nsubuga[1], Edridah Tukahebwa[3], Narcis B Kabatereine[3], Alison M Elliott[1,4], Emily L Webb[5], LaVIISWA trial team

Abstract
Background: Mass drug administration (MDA) is a cornerstone of control of parasitic helminths. In schistosomiasis-endemic areas with >50% of school-aged children infected, community-wide MDA with praziquantel is recommended by the World Health Organisation (WHO), with target coverage of >75%. Using data from a cluster-randomised trial of MDA treatment strategies, we aimed to describe the proportion of eligible residents who received MDA and predictors of treatment receipt, and to assess associations with helminth prevalence.
Methods: In the Koome islands of Lake Victoria, Uganda, where baseline schistosomiasis prevalence (by single stool sample, Kato Katz) was 52% overall (all ages) and 67% among school-aged children, we conducted a cluster-randomised trial of community-wide, intensive MDA (quarterly single-dose praziquantel 40mg/kg; triple-dose albendazole 400mg) versus standard, Uganda government intervention (annual single-dose praziquantel 40mg/kg; 6-monthly single-dose albendazole). Twenty-six fishing villages were randomised, 13 per trial arm, for four years. At each treatment round, praziquantel treatment and the first dose of

albendazole treatment were directly observed by the study team, registers of village residents were updated and the proportion receiving treatment among those eligible recorded.
Results: During the four-year MDA, at each treatment round an average of 13,382 people were registered in the 26 villages (7,153 and 6,229 in standard and intensive intervention villages, respectively). Overall, the proportion of those eligible receiving praziquantel was lower than for albendazole (60% versus 65%), particularly in the standard arm (61% versus 71%) compared to the intensive arm (60% versus 62%). Albendazole receipt was lower when given concurrently with praziquantel. Absence was the commonest reason for non-receipt of treatment (81% albendazole, 77% praziquantel), followed by refusal (14% albendazole, 18% praziquantel). Proportions receiving treatment were lowest among school-aged children, but did not differ by sex. Longitudinal analysis of a subgroup of residents who did not move during the study period found that persistent non-receipt of treatment in this subgroup was rare. Refusal to receive treatment was highest among adults and more common among females.
Conclusion: In schistosomiasis high-risk communities, a combination of approaches to increasing treatment coverage, such as extended periods of treatment delivery, and the provision of incentives, may be required to achieve WHO targets.

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Baseline patterns of infection in regions of Benin, Malawi and India seeking to interrupt transmission of soil transmitted helminths (STH) in the DeWorm3 trial
DeWorm3 Trials Team
Abstract
Global efforts to control morbidity associated with soil-transmitted helminth infections (STH) have focused largely on the targeted treatment of high-risk groups, including children and pregnant women. However, it is not clear when such programs can be discontinued and there are concerns about the sustainability of current STH control programs. The DeWorm3 project is a large multi-country community cluster randomized trial in Benin, India and Malawi designed to determine the feasibility of interrupting the transmission of STH using community-wide delivery of mass drug administration (MDA) with anthelmintics over multiple rounds. Here, we present baseline data and estimate key epidemiological parameters important in determining the likelihood of transmission interruption in the DeWorm3 trial. A baseline census was conducted in October-December 2017 in India, November-December 2017 in Malawi and in January-February 2018 in Benin. The baseline census enumerated all members of each household and collected demographic data and information on occupation, assets, and access to water, sanitation and hygiene (WASH). Each study site was divided into 40 clusters of at least 1,650 individuals per cluster. Clusters were randomized to receive twice yearly community-wide MDA with albendazole (GSK) targeting eligible individuals of all ages (20 clusters), or to receive the standard-of-care deworming program targeting children provided in each country. In each site, a randomly selected group of 150 individuals per cluster (6,000 total per site) was selected from the baseline census using stratified random sampling, and each individual provided a single stool sample for

analysis of STH infection using the Kato-Katz technique. Study site, household and individual characteristics were summarized as appropriate. We estimated key epidemiological parameters including the force of infection and the degree of parasite aggregation within the population. The DeWorm3 sites range in population from 94,969 to 140,932. The population age distribution varied significantly by site, with the highest proportion of infants and young children in Malawi and the highest proportion of adults in India. The baseline age- and cluster-weighted prevalence, as measured by Kato-Katz, varied across sites and by species, Baseline hookworm prevalence in India was 21.4% (95% CI: 20.4-22.4%), while prevalence of Ascaris and Trichuris by Kato-Katz was low (0.1% and 0.3% overall). In Malawi, the overall age- and cluster-weighted STH prevalence was 7.7% (95% CI: 7.1-8.4%) predominantly driven by hookworm infections (7.4%) while Ascaris (0.1%) and Trichuris (0.3%) infections were rare. In Benin, the overall age- and cluster-weighted prevalence was significantly lower (5.6%, 95% CI: 5.1-6.2%) and Ascaris (2.0%, 95% CI: 1.6-2.3%) was more common than in other sites. Ascaris infections were more likely to be moderate- or heavy-intensity (43.7%, unweighted) compared to hookworm (5.0%). The force of infection for hookworm was highest in adults in India and Malawi but appeared relatively stable across age groups in Benin. These data demonstrate the significant variability between the sites in terms of demography, socio-economic status and environmental characteristics. In addition, the baseline prevalence and intensity data from DeWorm3 suggest that each site has unique epidemiologic characteristics that will be critical in determining correlates of achieving STH transmission interruption in the DeWorm3 trial.

Lancet Glob Health. 2020 Nov;8(11):e1418-e1426.
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Patterns of individual non-treatment during multiple rounds of mass drug administration for control of soil-transmitted helminths in the TUMIKIA trial, Kenya: a secondary longitudinal analysis

William E Oswald[1], Stella Kepha[2], Katherine E Halliday[3], Carlos Mcharo[4], Th'uva Safari[4], Stefan Witek-McManus[3], Robert J Hardwick[5], Elizabeth Allen[6], Sultani H Matendechero[7], Simon J Brooker[3], Sammy M Njenga[4], Charles S Mwandawiro[4], Roy M Anderson[5], Rachel L Pullan[3]

Abstract

Background: Few studies have been done of patterns of treatment during mass drug administration (MDA) to control neglected tropical diseases. We used routinely collected individual-level treatment records that had been collated for the Tuangamize Minyoo Kenya Imarisha Afya (Swahili for Eradicate Worms in Kenya for Better Health [TUMIKIA]) trial, done in coastal Kenya from 2015 to 2017. In this analysis we estimate the extent of and factors associated with the same individuals not being treated over multiple rounds of MDA, which we term systematic non-treatment.

Methods: We linked the baseline population of the TUMIKIA trial randomly assigned to receive biannual community-wide MDA for soil-transmitted helminthiasis to longitudinal records on receipt of treatment in any of the four treatment rounds of the study. We fitted logistic regression models to estimate the association of non-treatment in a given round with non-treatment in the previous round, controlling for identified predictors of non-treatment.

We also used multinomial logistic regression to identify factors associated with part or no treatment versus complete treatment.
Findings: 36 327 participants were included in our analysis: 16 236 children aged 2-14 years and 20 091 adults aged 15 years or older. The odds of having no treatment recorded was higher if a participant was not treated during the previous round of MDA (adjusted odds ratio [OR] 3·60, 95% CI 3·08-4·20 for children and 5·58, 5·01-6·21 for adults). For children, school attendance and rural residence reduced the odds of receiving part or no treatment, whereas odds were increased by least poor socioeconomic status and living in an urban or periurban household. Women had higher odds than men of receiving part or no treatment. However, when those with pregnancy or childbirth in the previous 2 weeks were excluded, women became more likely to receive complete treatment. Adults aged 20-25 years were the age group with the highest odds of receiving part (OR 1·41, 95% CI 1·22-1·63) or no treatment (OR 1·81, 95% CI 1·53-2·14).
Interpretation: Non-treatment was associated with specific sociodemographic groups and characteristics and did not occcur at random. This finding has important implications for MDA programme effectiveness, the relevance of which will intensify as disease prevalence decreases and infections become increasingly clustered.

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Household finished flooring and soil-transmitted helminth and Giardia infections among children in rural Bangladesh and Kenya: a prospective cohort study
Jade Benjamin-Chung[1], Yoshika S Crider[2], Andrew Mertens[3], Ayse Ercumen[4], Amy J Pickering[5], Audrie Lin[3], Lauren Steinbaum[6], Jenna Swarthout[5], Mahbubur Rahman[7], Sarker M Parvez[7], Rashidul Haque[7], Sammy M Njenga[8], Jimmy Kihara[8], Clair Null[9], Stephen P Luby[10], John M Colford Jr[3], Benjamin F Arnold[11]
Abstract
Background: Soil-transmitted helminths and Giardia duodenalis are responsible for a large burden of disease globally. In low-resource settings, household finished floors (eg, concrete floors) might reduce transmission of soil-transmitted helminths and G duodenalis.
Methods: In a prospective cohort of children nested within two randomised trials in rural Bangladesh and Kenya, we estimated associations between household finished flooring and soil-transmitted helminths and G duodenalis prevalence. In 2015-16, we collected stool samples from children aged 2-16 years in rural Bangladesh and Kenya. We detected soil-transmitted helminth infection using quantitative PCR (qPCR; Bangladesh n=2800; Kenya n=3094), and G duodenalis using qPCR in Bangladesh (n=6894) and ELISA in Kenya (n=8899). We estimated adjusted prevalence ratios (aPRs) using log-linear models adjusted for potential confounders.
Findings: 7187 (92·2%) of 7795 children in Bangladesh and 9077 (93·7%) of 9686 children in Kenya provided stool specimens that were analysed by qPCR. At enrolment, 691 (10%) households in Bangladesh and 471 (5%) households in Kenya had finished floors. In both countries, household finished flooring was associated with lower Ascaris lumbricoides prevalence (Bangladesh aPR 0·33, 95% CI 0·14-0·78; Kenya 0·62, 0·39-0·98) and any soil-transmitted helminths (Bangladesh 0·73, 0·52-1·01; Kenya 0·57, 0·37-0·88). Household finished floors were also associated with lower Necator americanus prevalence in

Bangladesh (0·52, 0·29-0·94) and G duodenalis prevalence in both countries (Bangladesh 0·78, 0·64-0·95; Kenya 0·82, 0·70-0·97).
Interpretation: In low-resource settings, living in households with finished floors over a 2-year period was associated with lower prevalence of G duodenalis and some soil-transmitted helminths in children.

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doi: 10.1186/s13071-020-04572-7.

Forecasting the effectiveness of the DeWorm3 trial in interrupting the transmission of soil-transmitted helminths in three study sites in Benin, India and Malawi

James E Truscott[1 2 3], Robert J Hardwick[4 5 6], Marleen Werkman[4 5 7], Puthupalayam Kaliappan Saravanakumar[8], Malathi Manuel[8], Sitara S R Ajjampur[8], Kristjana H Ásbjörnsdóttir[6 9], Kalua Khumbo[10], Stefan Witek-McManus[11], James Simwanza[10], Gilles Cottrell[12], Parfait Houngbégnon[13], Moudachirou Ibikounlé[13 14], Judd L Walson[4 6 9], Roy M Anderson[4 5 6]

Abstract

Background: The DeWorm3 project is an ongoing cluster-randomised trial assessing the feasibility of interrupting the transmission of soil-transmitted helminths (STH) through mass drug administration (MDA) using study sites in India, Malawi and Benin. In this article, we describe an approach which uses a combination of statistical and mathematical methods to forecast the outcome of the trial with respect to its stated goal of reducing the prevalence of infection to below 2%.
Methods: Our approach is first to define the local patterns of transmission within each study site, which is achieved by statistical inference of key epidemiological parameters using the baseline epidemiological measures of age-related prevalence and intensity of STH infection which have been collected by the DeWorm3 trials team. We use these inferred parameters to calibrate an individual-based stochastic simulation of the trial at the cluster and study site level, which is subsequently run to forecast the future prevalence of STH infections. The simulator takes into account both the uncertainties in parameter estimation and the variability inherent in epidemiological and demographic processes in the simulator. We interpret the forecast results from our simulation with reference to the stated goal of the DeWorm3 trial, to achieve a target of [Formula: see text] prevalence at a point 24 months post-cessation of MDA.
Results: Simulated output predicts that the two arms will be distinguishable from each other in all three country sites at the study end point. In India and Malawi, measured prevalence in the intervention arm is below the threshold with a high probability (90% and 95%, respectively), but in Benin the heterogeneity between clusters prevents the arm prevalence from being reduced below the threshold value. At the level of individual study arms within each site, heterogeneity among clusters leads to a very low probability of achieving complete elimination in an intervention arm, yielding a post-study scenario with widespread elimination but a few 'hot spot' areas of persisting STH transmission.
Conclusions: Our results suggest that geographical heterogeneities in transmission intensity and worm aggregation have a large impact on the effect of MDA. It is important to accurately assess cluster-level, or even smaller scale, heterogeneities in factors which influence transmission and aggregation for a clearer perspective on projecting the outcomes of MDA control of STH and other neglected tropical diseases.

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Hand hygiene intervention to optimize helminth infection control: Design and baseline results of Mikono Safi-An ongoing school-based cluster-randomised controlled trial in NW Tanzania

Kenneth Makata[1], Safari Kinung'hi[2], Christian Hansen[3], Philip Ayieko[1 3], Simon Sichalwe[1], Onike Mcharo[1], Jeroen Ensink[4], Robert Dreibelbis[4], Sarah Rockowitz[5], Elialilia Okello[1], Heiner Grosskurth[1 2 3], Saidi Kapiga[1 2 3]

Abstract

Introduction: Soil transmitted helminths (STH) can affect over 50% of children in some parts of Tanzania. Control measures involve annual deworming campaigns in schools, but re-infection is rapid. This paper presents the design and baseline survey results of an ongoing school-based cluster-randomised controlled trial in Kagera region, NW Tanzania. The trial aims to determine whether the effect of routine deworming on the prevalence of Ascaris lumbricoides and Trichuris trichiura infections among school aged children can be sustained when combined with a behaviour change intervention promoting handwashing with water and soap.

Methods: As part of the trial, a total of 16 schools were randomised to receive the intervention (N = 8) or as controls (N = 8). Randomisation was stratified per district and restricted to ensure pre-trial STH prevalence was balanced between study arms. The combination intervention to be tested comprises class-room based teacher-led health education, improvement of handwash stations, coloured nudges to facilitate handwashing and parental engagement sessions. The impact evaluation involves two cross-sectional surveys conducted at baseline and endline. The objectives of the baseline survey were: (i) to confirm whether the deworming campaign was successful, and identify and treat students still infected about 2 weeks after deworming, (ii) to document any baseline differences in STH prevalence between trial arms, and (iii) to assess handwashing behaviours, and access to water and sanitation at school and home. We randomly sampled 35 students per class in Grades 1-6 (an average of 200 children per school), stratified to ensure equal representation between genders. Assenting students were interviewed using a structured questionnaire and asked to provide a stool specimen.

Results: Results of the baseline survey conducted about 2 weeks after deworming shows balanced demographic and STH prevalence data across trial arms. We observed a low prevalence of ascariasis (< 5%) as expected; however, the prevalence of trichuriasis was still about 35% in both arms.

Conclusion: The randomisation procedure was successful in achieving a balanced distribution of demographic characteristics and helminth infections between trial arms. The intervention is being rolled out. The current deworming treatment regimen may need to be revised with regards to the treatment of trichuriasis.

Sci Rep. 2020 Nov 4;10(1):19023. doi: 10.1038/s41598-020-75781-4.

Effect of anthelmintic treatment on serum free IGF-1 and IGFBP-3: a cluster-randomized-controlled trial in Indonesia

Farid Kurniawan[1 2 3], Dicky L Tahapary[4 5], Karin de Ruiter[3], Em Yunir[1 2], Nienke R Biermasz[6], Johannes W A Smit[7 8], Taniawati Supali[9], Erliyani Sartono[3], Maria Yazdanbakhsh[3], Pradana Soewondo[1 2]

Abstract

In children, soil-transmitted helminth infections have been linked to poor nutritional status and growth retardation in association with lower levels of IGF-1. In adults, IGF-1 has an anabolic and metabolic function and is related to nutritional status. Here, we assessed the impact of helminth infection on free IGF-1 and its major binding protein, IGFBP-3, in adults. The levels of IGF-1 and IGFBP3 were measured in 1669 subjects aged ≥ 16 years, before and after receiving four rounds of albendazole 400 mg/day or matching placebo for three consecutive days. Helminth infection status was assessed by microscopy (Kato-Katz) and PCR. Serum free IGF-1 level was significantly lower in helminth-infected subjects [mean difference and 95% CI - 0.068 (- 0.103; - 0.033), P < 0.001 after adjustment for age, sex, body mass index, and fasting insulin level]. There was no difference in IGFBP-3 level between helminth infected versus non-infected subjects. In the whole study population, albendazole treatment significantly increased serum free IGF-1 level [estimate and 95% CI 0.031 (0.004; - 0.057), P = 0.024] whereas no effect was found on the IGFBP-3 level. Our study showed that helminth infection in adults is associated with lower free IGF-1 levels but not with IGFBP-3 and albendazole treatment significantly increases free IGF-1 levels in the study population.

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The impact of Worms and Ladders, an innovative health educational board game on Soil-Transmitted Helminthiasis control in Abeokuta, Southwest Nigeria

Dorcas B Bassey[1], Hammed O Mogaji[2], Gabriel A Dedeke[1], Bolanle I Akeredolu-Ale[3], Eniola M Abe[4], Akinola S Oluwole[5], Abdulhakeem A Adeniran[1 6], Olagunju A Agboola[1 7], Chiedu F Mafiana[8], Uwem F Ekpo[1]

Abstract

In most endemic sub-Saharan African countries, repeated infections with soil-transmitted helminth (STH) occur as early as six weeks after the end of mass drug administration (MDA) with albendazole. In this study, we designed a new health educational board game Worms and Ladders and evaluated its potential to complement MDA with albendazole and reduce reinfection rates through the promotion of good hygiene practices among school-aged children. The evaluation employed a randomized control trial (RCT) design. Baseline knowledge, attitude and practices (KAP) relating to STH were obtained using a questionnaire from 372 pupils across six schools in Abeokuta, Nigeria. Schools were randomly assigned into intervention and control group, with the former and latter receiving Worms and Ladders and the common Snake and Ladder board game respectively. Fresh stool samples were also collected at baseline for STH diagnosis before administering 400mg single dose albendazole. Follow-up assessments of STH burden and KAP were conducted three and six months' post-intervention. Data generated from the study were analyzed using SPSS 20.0 software, with confidence interval set at 95%. Prevalence of STH dropped from 25.0% to 10.4% in the intervention group and 49.4% to 33.3% in the control group at three months' post-intervention. The prevalence further dropped to 5.6% in the intervention group at six months' post-intervention. However, it increased to 37.2% in the control group at six

months' post-intervention. There was a significant difference ($p<0.05$) in prevalence after intervention among the groups. KAP on transmission, control and prevention of STH significantly improved ($p<0.05$) from 5.2% to 97.9% in the intervention group compared to 6.2% to 7.1% in the control group. The Worms and Ladders board game shows the potential to teach and promote good hygiene behavior among SAC. These findings posit the newly developed game as a reliable tool to complement mass drug administration campaigns for STH control.

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Effects of nutritional supplements on the re-infection rate of soil-transmitted helminths in school-age children: A systematic review and meta-analysis

Aisha Ummi Jibrin Isah[1], Obinna Ikechukwu Ekwunife[2], Izuchukwu Loveth Ejie[2], Olena Mandrik[1]

Abstract

Background: The effect of nutritional supplements on the re-infection rate of species-specific soil-transmitted helminth infections in school-aged children remains complex and available evidence on the subject matter has not been synthesized.

Methods: The review included randomised controlled trials (RCTs) and cluster RCTs investigating food supplements on school-aged children between the age of 4-17 years. A search for RCTs was conducted on eight databases from inception to 12th June 2019. Cochrane Risk of Bias tool was used to assess the risk of bias in all included studies. Meta-analysis and narrative synthesis were conducted to describe and analyze the results of the review. Outcomes were summarized using the mean difference or standardized mean difference where appropriate.

Results: The search produced 1,816 records. Six studies met the inclusion criteria (five individually RCTs and one cluster RCT). Four studies reported data on all three STH species, while one study only reported data on Ascaris lumbricoides infections and the last study reported data on only hookworm infections. Overall, the risk of bias in four individual studies was low across most domains. Nutritional supplementation failed to statistically reduce the re-infection rates of the three STH species. The effect of nutritional supplements on measures of physical wellbeing in school-aged children could not be determined.

Conclusions: The findings from this systematic review suggest that nutritional supplements for treatment of STH in children should not be encouraged unless better evidence emerges. Conclusion of earlier reviews on general populations may not necessarily apply to children since children possibly have a higher re-infection rate.

Cochrane Database Syst Rev. 2021 May 17;5(5):CD005547.
doi: 10.1002/14651858.CD005547.pub4.

Effect of mass deworming with antihelminthics for soil-transmitted helminths during pregnancy

Rehana A Salam[1], Jai K Das[1], Zulfiqar A Bhutta[2]

Abstract

Background: Helminthiasis is an infestation of the human body with parasitic worms. It is estimated to affect 44 million pregnancies, globally, each year. Intestinal helminthiasis (hookworm infestation) is associated with blood loss and decreased supply of nutrients for erythropoiesis, resulting in iron-deficiency anaemia. Over 50% of the pregnant women in low- and middle-income countries (LMIC) suffer from iron-deficiency anaemia. Though iron-deficiency anaemia is multifactorial, hookworm infestation is a major contributory cause in women of reproductive age in endemic areas. Antihelminthics are highly efficacious, but evidence of their beneficial effect and safety when given during pregnancy has not been established. This is an update of a Cochrane Review last published in 2015.
Objectives: To determine the effects of mass deworming with antihelminthics for soil-transmitted helminths (STH) during the second or third trimester of pregnancy on maternal and pregnancy outcomes.
Search methods: For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP) (8 March 2021) and reference lists of retrieved studies.
Selection criteria: We included all prospective randomised controlled trials evaluating the effect of administration of antihelminthics versus placebo or no treatment during the second or third trimester of pregnancy; both individual-randomised and cluster-randomised trials were eligible. We excluded quasi-randomised trials and studies that were only available as abstracts with insufficient information.
Data collection and analysis: Two review authors independently assessed trials for inclusion and risk of bias, extracted data, checked accuracy and assessed the certainty of the evidence using the GRADE approach.
Main results: We included a total of six trials (24 reports) that randomised 7873 pregnant women. All of the included trials were conducted in antenatal clinics within hospitals in LMICs (Uganda, Nigeria, Peru, India, Sierra Leone and Tanzania). Among primary outcomes, five trials reported maternal anaemia, one trial reported preterm birth and three trials reported perinatal mortality. Among secondary outcomes, included trials reported maternal worm prevalence, low birthweight (LBW) and birthweight. None of the included studies reported maternal anthropometric measures or infant survival at six months. Overall, we judged the included trials to be generally at low risk of bias for most domains, while the certainty of evidence ranged from low to moderate. Analysis suggests that administration of a single dose of antihelminthics in the second trimester of pregnancy may reduce maternal anaemia by 15% (average risk ratio (RR) 0.85, 95% confidence interval (CI) 0.72 to 1.00; I^2= 86%; 5 trials, 5745 participants; low-certainty evidence). We are uncertain of the effect of antihelminthics during pregnancy on preterm birth (RR 0.84, 95% CI 0.38 to 1.86; 1 trial, 1042 participants; low-certainty evidence) or perinatal mortality (RR 1.01, 95% CI 0.67 to 1.52; 3 trials, 3356 participants; low-certainty evidence). We are uncertain of the effect of antihelminthics during pregnancy on hookworm (average RR 0.31, 95% CI 0.05 to 1.93; Tau^2 = 1.76, I^2 = 99%; 2 trials, 2488 participants; low-certainty evidence). Among other secondary outcomes, findings suggest that administration of antihelminthics during pregnancy may reduce the prevalence of trichuris (average RR 0.68, 95% CI 0.48 to 0.98; I^2=75%; 2 trials, 2488 participants; low-certainty evidence) and ascaris (RR 0.24, 95% CI 0.19 to 0.29; I^2= 0%; 2 trials, 2488 participants; moderate-certainty evidence). Antihelminthics during pregnancy probably make little or no difference to LBW (RR 0.89, 95% CI 0.69 to 1.16; 3 trials, 2960 participants; moderate-certainty evidence) and birthweight (mean difference 0.00 kg, 95% CI -0.03 kg to 0.04 kg; 3 trials, 2960 participants; moderate-certainty evidence).

Authors' conclusions: The evidence suggests that administration of a single dose of antihelminthics in the second trimester of pregnancy may reduce maternal anaemia and worm prevalence when used in settings with high prevalence of maternal helminthiasis. Further data is needed to establish the benefit of antihelminthic treatment on other maternal and pregnancy outcomes. Future research should focus on evaluating the effect of these antihelminthics among various subgroups in order to assess whether the effect varies. Future studies could also assess the effectiveness of co-interventions and health education along with antihelminthics for maternal and pregnancy outcomes.

Hepatitis

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doi: 10.1136/gutjnl-2020-322719. Online ahead of print.

Long-term safety of infants from mothers with chronic hepatitis B treated with tenofovir disoproxil in China

Calvin Q Pan[1,2], Erhei Dai[3], Zhongping Duan[4], Guorong Han[5], Wenjing Zhao[6], Yuming Wang[7], Huaihong Zhang[8], Baoshen Zhu[9], Hongxiu Jiang[5], Shuqin Zhang[10], Xiaohu Zhang[8], Huaibin Zou[4], Xiuli Chen[3], Yu Chen[4]

Abstract

Objective: The physical and neuromental development of infants remains uncertain after fetal exposure to tenofovir disoproxil fumarate (TDF) for the prevention of mother-to-child transmission of HBV. We aimed to investigate the safety of TDF therapy during the third trimester of pregnancy.

Design: Infants from a previous randomised controlled trial were recruited for our long-term follow-up (LTFU) study. Mothers with chronic hepatitis B were randomised to receive TDF therapy or no treatment during the third trimester. Infants' physical growth or malformation, bone mineral density (BMD) and neurodevelopment, as assessed using Bayley-III assessment, were examined at 192 weeks of age.

Results: Of 180 eligible infants, 176/180 (98%) were enrolled and 145/176 (82%) completed the LTFU (control group: 75; TDF-treated group: 70). In the TDF-treated group, the mean duration of fetal exposure to TDF was 8.57±0.53 weeks. Congenital malformation rates were similar between the two groups at week 192. The mean body weight of boys in the control and TDF-treated groups was significantly higher (19.84±3.46 kg vs. 18.47±2.34 kg; p=0.03) and within the normal range (18.48±2.35 kg vs. 17.80±2.50 kg; p=0.07), respectively, when compared with the national standard. Other prespecified outcomes (head circumference, height, BMD, and cognitive, motor, social-emotional, and adaptive behaviour measurements) were all comparable between the groups.

Conclusion: Infants with fetal exposure to TDF had normal physical growth, BMD and neurodevelopment at week 192. Our findings provide evidence on the long-term safety of infants after fetal exposure to maternal TDF therapy for preventing hepatitis B transmission.

Rev Med Virol. 2021 Jan 10;e2216.
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Tenofovir disoproxil fumarate for prevention of mother-to-child transmission of hepatitis B virus: A systematic review and meta-analysis of randomised control trials

Eden Dagnachew Zeleke[1,2], Dawit Getachew Assefa[1,3], Michele Joseph[1], Delayehu Bekele[1,4], Hanna Amanuel Tesfahunei[1,5], Emnet Getachew[1,6], Tsegahun Manyazewal[1]

Abstract

Hepatitis B virus (HBV) infection caused by mother-to-child transmission (MTCT) continues to pose challenges to global health. This study aimed to assess the efficacy and safety of tenofovir disoproxil fumarate (TDF) for preventing HBV MTCT. PubMed and the Cochrane Central Register of Controlled Trials were searched through August 2020. Randomised controlled trials (RCTs) were selected that evaluated the efficacy and safety of TDF for preventing MTCT of HBV compared with the standard of care, placebo or other HBV therapies. The primary outcomes were HBV MTCT rate and maternal HBV DNA level. Secondary outcomes were infant and maternal safety outcomes. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines, and prospectively registered on PROSPERO (CRD42020186275). Of 240 citations, three RCTs that involved 651 participants were included. The pooled result showed that TDF can reduce the risk of HBV MTCT after 6 months postpartum by 80% (risk ratio [RR] 0.2, 95% confidence interval [CI 0.06-0.7], n = 584) with low heterogeneity (I^2 = 0%). TDF demonstrated HBV DNA suppression at delivery, though there was heterogeneity among individual studies (RR 0.13, 95% CI [0.08-0.20] and (RR 0.36, 95% CI [0.27-0.49]). Maternal and infant safety outcomes were comparable among treated and untreated mothers and infants born to them. The quality of evidence varied from high to very low. There is evidence that TDF effectively interrupted MTCT of HBV and suppressed HBV DNA level. Available studies on safety are very limited and heterogeneous, emphasising the need for additional RCTs with complete safety indicators.

Hypoglycaemia

Lancet Glob Health. 2020 Dec;8(12):e1546-e1554.
doi: 10.1016/S2214-109X(20)30388-0. Epub 2020 Oct 8.

Effect on mortality of increasing the cutoff blood glucose concentration for initiating hypoglycaemia treatment in severely sick children aged 1 month to 5 years in Malawi (SugarFACT): a pragmatic, randomised controlled trial

Tim Baker[1], Fatsani Ngwalangwa[2], Henderson Masanjala[3], Queen Dube[3], Josephine Langton[4], Gaetano Marrone[5], Helena Hildenwall[6]

Abstract

Background: Low blood glucose concentrations are common in sick children who present to hospital in low-resource settings and are associated with increased mortality. The cutoff blood glucose concentration for the diagnosis and treatment of hypoglycaemia currently recommended by WHO (2·5 mmol/L) is not evidence-based. We aimed to assess whether increasing the cutoff blood glucose concentration for hypoglycaemia treatment in severely ill children at presentation to hospital improves mortality outcomes.

Methods: We did a pragmatic, randomised controlled trial at two referral hospitals in Malawi. Severely ill children aged 1 month to 5 years presenting to the emergency

department with a capillary blood glucose concentration of between 2·5 mmol/L (3·0 mmol/L in severely malnourished children) and 5·0 mmol/L were randomly assigned (1:1) by a computer-generated randomisation sequence, stratified by study site and severe malnutrition, to receive either an immediate intravenous bolus of 10% dextrose at 5 mL/kg followed by a 24-h maintenance infusion of 10% dextrose at 100 mL/kg for the first 10 kg of bodyweight, 50 mL/kg for the next 10 kg, and 20 mL/kg for each subsequent kg of bodyweight (intervention group) or observation for a minimum of 60 min and standard care (control group). Participants and study personnel were not masked to treatment allocation. The primary outcome was all-cause in-hospital mortality, assessed on an intention-to-treat basis. Safety was also assessed in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT02989675.

Findings: Between Dec 5, 2016, and Jan 22, 2019, 10 947 children were screened, of whom 332 were randomly assigned, and 322 were included in the final analysis (n=162 in the control group and n=160 in the intervention group). The study was terminated after an interim analysis at 24% enrolment indicated futility. The median age of participants was 2·3 years (IQR 1·4-3·2), 65 (45%) were female, and the baseline characteristics of participants were similar between the two groups. The number of in-hospital deaths from any cause was 26 (16%) in the control group and 24 (15%) in the intervention group, with an absolute mortality difference of 1·0% (95% CI -6·9 to 9·0). Serious adverse events, including hypoglycaemia, hyperglycaemia, convulsions, reduced consciousness, and death, were reported in 47 (29%) children in the control group and 39 (24%) children in the intervention group.

Interpretation: Increasing the cutoff blood glucose concentration for hypoglycaemia treatment in severely sick children in Malawi from 2·5 mmol/L to 5·0 mmol/L did not reduce all-cause in-hospital mortality. Our findings do not support changing the cutoff for dextrose administration, and further research on the optimal management of severely ill children who present to the emergency department with low blood glucose concentrations is warranted.

Injury prevention

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Online ahead of print.

Effectiveness of School-Based Interventions in Reducing Unintentional Childhood Injuries-A Cluster Randomized Trial

Ramesh Holla[1], B B Darshan[2], Bhaskaran Unnikrishnan[2], Nithin Kumar[2], Anju Sinha[3], Rekha Thapar[2], P Prasanna Mithra[2], Vaman Kulkarni[2], Archana Ganapathy[2], Himani Kotian[2]

Abstract

Background: Unintentional injuries cause up to 950,000 deaths among children under 18 years worldwide annually.

Objectives: To evaluate the effectiveness of school based interventions in promoting child safety and reducing unintentional childhood injuries.

Methods: This Cluster randomised trial with 1:1 allocation of clusters to intervention and control arm was conducted in the public and private schools of Dakshina Kannada district, Karnataka, over a period of 10 months. Study participants included children from standard

5-7 in schools selected for the study. 10 schools that could accommodate 1100 students each, were randomly allocated to the interventional and control arm. A comprehensive child safety and injury prevention module was developed based on the opinions of school teachers through focus group discussions. This module was periodically taught to the students of intervention arm by the teachers. The children in control arm did not receive any intervention. Outcome was assessed by determining the incidence of unintentional injuries and type of injuries from the questionnaire used at the baseline, and at the end of three, six, and ten months.
Result: Unintentional injuries declined progressively from baseline until the end of the study in both the interventional arm (from 52.9% to 2.5%) and control arm (from 44.7% to 32%) [AOR (95% CI) 0.458 (0.405 - 0.518); P value <0.0001]. The decline in incidence of injuries in the interventional arm was higher than that in the control arm (50.4% vs 12.7%; P <0.0001).
Conclusion: School based educational intervention using child safety and injury prevention modules is effective in reducing unintentional injuries among school children over a 10-month period.

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Effect of a Home Safety Supervisory Program on Occurrence of Childhood Injuries: A Cluster Randomized Controlled Trial
Anice George[1], G Renu[2], Sheela Shetty[3]
Abstract
Objectives: To evaluate the effect of home safety supervisory program on improvement in childhood safety, self-reported home hazard of caregivers, and caregivers' supervisory attitude.
Design: Randomized controlled trial.
Setting and subject: Caregivers of children between 2 to 5 years of age residing in selected villages in Karnataka.
Intervention: Intervention group was administered Home safety supervisory program (HSSP), whereas the control group received teaching on child care.
Result: The intervention group had a significant reduction in the frequency of childhood injuries when compared with the control group [MD (95% CI) 8.96 vs 3.37], after the administration of Home safety supervisory program. There was a significant difference in the mean baseline scores of caregivers self-reported home hazard practices between the two groups (P<0.001), and improvement in the supervisory attitudes of caregivers in the intervention group (P<0.001).
Conclusion: Appropriate and effective home hazard reduction teaching reduces home injuries in children. The improved awareness of caregivers in child safety, and child supervision emphasizes the importance of this program.

Infection control

Arch Dis Child Fetal Neonatal Ed. 2021 Jun 9;fetalneonatal-2020-321174.
doi: 10.1136/archdischild-2020-321174. Online ahead of print.

Integrated management of Childhood Illness (IMCI)

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Integrated community case management of childhood illness in low- and middle-income countries

Nicholas P Oliphant[1,2], Samuel Manda[3,4], Karen Daniels[5,6], Willem A Odendaal[5], Donela Besada[5], Mary Kinney[1], Emily White Johansson[7], Tanya Doherty[5,2]

Abstract

Background: The leading causes of mortality globally in children younger than five years of age (under-fives), and particularly in the regions of sub-Saharan Africa (SSA) and Southern Asia, in 2018 were infectious diseases, including pneumonia (15%), diarrhoea (8%), malaria (5%) and newborn sepsis (7%) (UNICEF 2019). Nutrition-related factors contributed to 45% of under-five deaths (UNICEF 2019). World Health Organization (WHO) and United Nations Children's Fund (UNICEF), in collaboration with other development partners, have developed an approach - now known as integrated community case management (iCCM) - to bring treatment services for children 'closer to home'. The iCCM approach provides integrated case management services for two or more illnesses - including diarrhoea, pneumonia, malaria, severe acute malnutrition or neonatal sepsis - among under-fives at community level (i.e. outside of healthcare facilities) by lay health workers where there is limited access to health facility-based case management services (WHO/UNICEF 2012).

Objectives: To assess the effects of the integrated community case management (iCCM) strategy on coverage of appropriate treatment for childhood illness by an appropriate provider, quality of care, case load or severity of illness at health facilities, mortality, adverse events and coverage of careseeking for children younger than five years of age in low- and middle-income countries.

Search methods: We searched CENTRAL, MEDLINE, Embase and CINAHL on 7 November 2019, Virtual Health Library on 8 November 2019, and Popline on 5 December 2018, three other databases on 22 March 2019 and two trial registers on 8 November 2019. We performed reference checking, and citation searching, and contacted study authors to identify additional studies.

Selection criteria: Randomized controlled trials (RCTs), cluster-RCTs, controlled before-after studies (CBAs), interrupted time series (ITS) studies and repeated measures studies comparing generic WHO/UNICEF iCCM (or local adaptation thereof) for at least two iCCM diseases with usual facility services (facility treatment services) with or without single disease community case management (CCM). We included studies reporting on coverage of appropriate treatment for childhood illness by an appropriate provider, quality of care, case load or severity of illness at health facilities, mortality, adverse events and coverage of careseeking for under-fives in low- and middle-income countries.

Data collection and analysis: At least two review authors independently screened abstracts, screened full texts and extracted data using a standardised data collection form adapted from the EPOC Good Practice Data Collection Form. We resolved any disagreements through discussion or, if required, we consulted a third review author not involved in the original screening. We contacted study authors for clarification or additional details when necessary. We reported risk ratios (RR) for dichotomous outcomes and hazard ratios (HR) for

time to event outcomes, with 95% confidence intervals (CI), adjusted for clustering, where possible. We used estimates of effect from the primary analysis reported by the investigators, where possible. We analysed the effects of randomized trials and other study types separately. We used the GRADE approach to assess the certainty of evidence.
Main results: We included seven studies, of which three were cluster RCTs and four were CBAs. Six of the seven studies were in SSA and one study was in Southern Asia. The iCCM components and inputs were fairly consistent across the seven studies with notable variation for the training and deployment component (e.g. on payment of iCCM providers) and the system component (e.g. on improving information systems). When compared to usual facility services, we are uncertain of the effect of iCCM on coverage of appropriate treatment from an appropriate provider for any iCCM illness (RR 0.96, 95% CI 0.77 to 1.19; 2 CBA studies, 5898 children; very low-certainty evidence). iCCM may have little to no effect on neonatal mortality (HR 1.01, 95% 0.73 to 1.28; 2 trials, 65,209 children; low-certainty evidence). We are uncertain of the effect of iCCM on infant mortality (HR 1.02, 95% CI 0.83 to 1.26; 2 trials, 60,480 children; very low-certainty evidence) and under-five mortality (HR 1.18, 95% CI 1.01 to 1.37; 1 trial, 4729 children; very low-certainty evidence). iCCM probably increases coverage of careseeking to an appropriate provider for any iCCM illness by 68% (RR 1.68, 95% CI 1.24 to 2.27; 2 trials, 9853 children; moderate-certainty evidence). None of the studies reported quality of care, severity of illness or adverse events for this comparison. When compared to usual facility services plus CCM for malaria, we are uncertain of the effect of iCCM on coverage of appropriate treatment from an appropriate provider for any iCCM illness (very low-certainty evidence) and iCCM may have little or no effect on careseeking to an appropriate provider for any iCCM illness (RR 1.06, 95% CI 0.97 to 1.17; 1 trial, 811 children; low-certainty evidence). None of the studies reported quality of care, case load or severity of illness at health facilities, mortality or adverse events for this comparison.
Authors' conclusions: iCCM probably increases coverage of careseeking to an appropriate provider for any iCCM illness. However, the evidence presented here underscores the importance of moving beyond training and deployment to valuing iCCM providers, strengthening health systems and engaging community systems.

BMC Health Serv Res. 2021 Apr 16;21(1):354.
doi: 10.1186/s12913-021-06317-3.

An Integrated eDiagnosis Approach (IeDA) versus standard IMCI for assessing and managing childhood illness in Burkina Faso: a stepped-wedge cluster randomised trial

Sophie Sarrassat[1], James J Lewis[2], Arsene S Some[3], Serge Somda[3], Simon Cousens[4], Karl Blanchet[4]

Abstract
Background: The Integrated eDiagnosis Approach (IeDA), centred on an electronic Clinical Decision Support System (eCDSS) developed in line with national Integrated Management of Childhood Illness (IMCI) guidelines, was implemented in primary health facilities of two regions of Burkina Faso. An evaluation was performed using a stepped-wedge cluster randomised design with the aim of determining whether the IeDA intervention increased Health Care Workers' (HCW) adherence to the IMCI guidelines.
Methods: Ten randomly selected facilities per district were visited at each step by two trained nurses: One observed under-five consultations and the second conducted a repeat

consultation. The primary outcomes were: overall adherence to clinical assessment tasks; overall correct classification ignoring the severity of the classifications; and overall correct prescription according to HCWs' classifications. Statistical comparisons between trial arms were performed on cluster/step-level summaries.
Results: On average, 54 and 79% of clinical assessment tasks were observed to be completed by HCWs in the control and intervention districts respectively (cluster-level mean difference = 29.9%; P-value = 0.002). The proportion of children for whom the validation nurses and the HCWs recorded the same classifications (ignoring the severity) was 73 and 79% in the control and intervention districts respectively (cluster-level mean difference = 10.1%; P-value = 0.004). The proportion of children who received correct prescriptions in accordance with HCWs' classifications were similar across arms, 78% in the control arm and 77% in the intervention arm (cluster-level mean difference = - 1.1%; P-value = 0.788).
Conclusion: The IeDA intervention improved substantially HCWs' adherence to IMCI's clinical assessment tasks, leading to some overall increase in correct classifications but to no overall improvement in correct prescriptions. The largest improvements tended to be observed for less common conditions. For more common conditions, HCWs in the control districts performed relatively well, thus limiting the scope to detect an overall impact.

Iodine deficiency

Kidney disease

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doi: 10.1093/ndt/gfaa369. Online ahead of print.
Determining the optimal cholecalciferol dosing regimen in children with CKD: a randomized controlled trial
Arpana Iyengar[1], Nivedita Kamath[1], Hamsa V Reddy[1], Jyoti Sharma[2], Jyoti Singhal[2], Susan Uthup[3], Sudha Ekambaram[4], Sumithra Selvam[1], Anja Rahn[5], Dagmar-C Fischer[5], Mandy Wan[6], Rukshana Shroff[6]
Abstract
Background and objectives: The optimal treatment regimen for correcting 25-hydroxyvitamin D (25OHD) deficiency in children with chronic kidney disease (CKD) is not known. We compared cholecalciferol dosing regimens for achieving and maintaining 25OHD concentrations ≥30ng/ml in children with CKD stages 2-4.
Design: An open-label multicenter randomized controlled trial randomized children with 25OHD concentrations<30ng/ml in 1:1:1 to oral cholecalciferol 3,000 IU daily, 25,000 IU weekly, or 100,000 IU monthly for 3-months (maximum 3 intensive courses).In those with 25OHD ≥30ng/ml 1,000IU cholecalciferol daily (maintenance course) was given for up to 9 months. Primary outcome was achieving 25OHD≥30 ng/ml at end of intensive phase treatment.
Results: 90 children were randomized to daily(n = 30), weekly(n = 29) or monthly(n = 31) treatment groups. At end of intensive phase, 70/90(77.8%) achieved 25OHD ≥30ng/ml; 25OHD concentrations were comparable between groups (median 44.3, 39.4, and 39.3 ng/ml for daily, weekly, and monthly groups respectively; p = 0.24) with no difference between

groups for time to achieve 25OHD ≥30ng/ml (p = 0.28). There was no change in calcium, phosphorus, and parathyroid hormone, but fibroblast growth factor 23(p = 0.002) and klotho(p = 0.001) concentrations significantly increased and were comparable in all treatment groups. Irrespective of dosing regimen, children with glomerular disease had 25OHD concentrations lower than non-glomerular disease (25.8 vs 41.8 ng/ml; p = 0.007). One child had 25OHD concentration of 134 ng/ml and 5.5% had hypercalcemia without symptoms of toxicity.
Conclusion: Intensive treatment with oral cholecalciferol as daily, weekly or monthly regimens achieved similar 25OHD concentrations between treatment groups without toxicity. Children with glomerular disease required higher doses of cholecalciferol compared to those with non-glomerular disease.

Clin J Am Soc Nephrol. 2021 Feb 8;16(2):225-232.
doi: 10.2215/CJN.06140420. Epub 2021 Jan 21.
Short-Duration Prednisolone in Children with Nephrotic Syndrome Relapse: A Noninferiority Randomized Controlled Trial
Deepika Kainth[1], Pankaj Hari[2], Aditi Sinha[1], Shivam Pandey[3], Arvind Bagga[1]
Abstract
Background and objectives: In children with nephrotic syndrome, steroids are the cornerstone of therapy for relapse. The adequate duration and dosage of steroids, however, have not been an active area of research, especially in children with infrequently relapsing nephrotic syndrome. This study investigated the efficacy of an abbreviated regimen for treatment of a relapse in this population.
Design, setting, participants, & measurements: In a single-center, open-label, randomized controlled trial, we evaluated the efficacy of prednisolone as a "short regimen" (40 mg/m^2 on alternate days for 2 weeks) compared with "standard regimen" (40 mg/m^2 on alternate days for 4 weeks) for children aged 1-16 years who achieved remission of a relapse. The primary outcome was the proportion of children developing frequent relapses or steroid dependence at 12 months.
Results: A total of 117 patients were enrolled and randomized to short (55) or standard (62) regimen. Fourteen (24%) patients in standard regimen and 12 (23%) in short regimen developed frequent relapses or steroid dependence over a period of 1 year (risk difference, -1%; 95% confidence interval, -15 to 16; *P*=0.90). A large 95% confidence interval crossed the proposed noninferiority margin. In a time to event analysis, there was no significant difference in the proportion of children developing frequent relapses or steroid dependence and time to outcome between the two groups (hazard ratio, 1.01; 95% confidence interval, 0.83 to 1.23; *P*=0.98). Time to relapse, relapse rate, and steroid-related adverse events were similar in both groups. Cumulative steroid exposure was significantly lower in the short regimen (risk difference, -541 mg/m^2; 95% confidence interval, -917 to -164 mg/m^2; *P*<0.001).
Conclusions: In children with infrequently relapsing nephrotic syndrome, a short steroid treatment for relapse resulted in a similar proportion of patients developing frequent relapses or steroid dependence; however, noninferiority of a short regimen was not established.

Leishmaniasis

(See vaccines)

Lymphatic filariasis

Leprosy

Malaria

Malaria diagnosis

Lancet Glob Health. 2021 Mar;9(3):e320-e330.
doi: 10.1016/S2214-109X(20)30508-8.

Social group and health-care provider interventions to increase the demand for malaria rapid diagnostic tests among community members in Ebonyi state, Nigeria: a cluster-randomised controlled trial

Ugwu I Omale[1], Benedict N Azuogu[2], Chihurumnanya Alo[2], Ugochukwu C Madubueze[3], Onyinyechukwu U Oka[4], Kingsley C Okeke[4], Ifeyinwa M Okafor[4], Rowland Utulu[5], Irene I Eze[2], Uduak E Akpan[4], Chijioke V Iloke[4], Anthonia O Nnubia[4], Ogechukwu C Anene[4], Chukwuka R Nnabu[6], Desi O Ibemesi[4]

Abstract

Background: The rate of diagnostic testing for malaria is still very low in Nigeria despite the scale-up of malaria rapid diagnostic test (MRDT) availability, following WHO's recommendation of universal diagnostic testing in 2010. We investigated whether a social group sensitisation and education intervention (social group intervention) and a social group intervention plus health-care provider training intervention would increase the demand (use or request, or both) for MRDTs among community members in Ebonyi state, Nigeria.

Methods: We did a three-arm, parallel, open-label, stratified cluster-randomised controlled trial in Ebonyi state, Nigeria, to evaluate the effects of two interventions compared with a control. We randomly assigned geographical clusters that were accessible (close to a road that was drivable even during the rainy seasons) and had at least one eligible public primary health facility and patent medicine vendor (those that offered MRDT services) in a 1:1:1 allocation to the control arm (receiving no intervention), social group arm (receiving sensitisation and education about MRDT), or social group plus provider arm (receiving the social group intervention plus provider training in health communication about MRDT). Investigators, participants (social groups, providers, respondents), and interviewers could not be masked to group assignments. The primary outcome was the proportion of children younger than 5 years with fever or malaria-like illness, in the 2 weeks preceding a household survey, who received an MRDT, and the coprimary outcome was the same outcome but among children aged 5 years and older (ie, up to and including 17 years) and adults (excluding pregnant women). The outcomes were measured at an individual level via

household surveys before the interventions and 3 months after the end of the interventions. All analyses were done using a cluster-level method on an intention-to-treat basis. This trial is registered with ISRCTN, number ISRCTN14046444.
Findings: We carried out eligibility screening and recruitment of participants (clusters, social groups, and providers) between July 2 and Sept 27, 2018. 34 clusters met the eligibility criteria and 18 were randomly selected to participate and randomly assigned to arms (six clusters per arm). A mean proportion of 40·6% (SD 14·5) of eligible children younger than 5 years in the control arm received an MRDT, versus 66·7% (11·7) in the social group arm (adjusted risk difference [aRD] 28·8%, 95% CI 21·9-35·7, p<0·0001) and 71·7% (19·8) in the social group plus provider arm (aRD 32·7%, 24·9-40·5, p<0·0001), with no significant difference between the social group arm and the social group plus provider arm. A mean proportion of 36·3% (18·5) of eligible children aged 5 years and older in the control arm received an MRDT, versus 60·7% (14·0) in the social group arm (aRD 25·6%, 16·8-34·4, p=0·0004), and 59·5% (18·3) in the social group plus provider arm (aRD 28·0%, 19·5-36·5, p=0·0002), with no significant difference between the social group arm and the social group plus provider arm.
Interpretation: The sensitisation and education of social groups about MRDTs can significantly increase the demand for MRDTs. This intervention is pragmatic and could be applied within malaria control or elimination programmes, in Nigeria and in other high-burden countries, to enhance diagnostic testing for patients suspected of having malaria.

Insecticide-treated bed nets

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doi: 10.1186/s41182-020-00276-x.
A preliminary study on designing a cluster randomized control trial of two new mosquito nets to prevent malaria parasite infection
Noboru Minakawa[1], James O Kongere[2 3], George O Sonye[4], Peter A Lutiali[2 3], Beatrice Awuor[4], Hitoshi Kawada[5], Rie Isozumi[5], Kyoko Futami[5]
Abstract
Background: Although long-lasting insecticidal nets (LLINs) are the most effective tool for preventing malaria parasite transmission, the nets have some limitations. For example, the increase of LLIN use has induced the rapid expansion of mosquito insecticide resistance. More than two persons often share one net, which increases the infection risk. To overcome these problems, two new mosquito nets were developed, one incorporating piperonyl butoxide and another covering ceilings and open eaves. We designed a cluster randomized controlled trial (cRCT) to evaluate these nets based on the information provided in the present preliminary study.
Results: Nearly 75% of the anopheline population in the study area in western Kenya was Anopheles gambiae s. l., and the remaining was Anopheles funestus s. l. More female anophelines were recorded in the western part of the study area. The number of anophelines increased with rainfall. We planned to have 80% power to detect a 50% reduction in female anophelines between the control group and each intervention group. The between-cluster coefficient of variance was 0.192. As the number of clusters was limited to 4 due to the size of the study area, the estimated cluster size was 7 spray catches with an alpha of 0.05. Of 1619

children tested, 626 (48%) were Plasmodium falciparum positive using a rapid diagnostic test (RDT). The prevalence was higher in the northwestern part of the study area. The number of children who slept under bed nets was 929 (71%). The P. falciparum RDT-positive prevalence (RDTpfPR) of net users was 45%, and that of non-users was 55% (OR 0.73; 95% CI 0.56, 0.95). Using 45% RDTpfPR of net users, we expected each intervention to reduce prevalence by 50%. The intracluster correlation coefficient was 0.053. With 80% power and an alpha of 0.05, the estimated cluster size was 116 children. Based on the distribution of children, we modified the boundaries of the clusters and established 300-m buffer zones along the boundaries to minimize a spillover effect.
Conclusions: The cRCT study design is feasible. As the number of clusters is limited, we will apply a two-stage procedure with the baseline data to evaluate each intervention.

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doi: 10.1186/s12936-020-03437-9.

Long-lasting insecticide-treated bed net ownership, utilization and associated factors among school-age children in Dara Mallo and Uba Debretsehay districts, Southern Ethiopia

Zerihun Zerdo[1,2], Hilde Bastiaens[3], Sibyl Anthierens[3], Fekadu Massebo[4], Matewos Masne[4], Gelila Biresaw[5], Misgun Shewangizaw[6], Abayneh Tunje[6], Yilma Chisha[6], Tsegaye Yohannes[5], Jean-Pierre Van Geertruyden[7]

Abstract

Background: Malaria is one of the major causes of morbidity and mortality among school-age children (SAC) in sub-Saharan Africa. SAC account for more than 60% of the reservoir of malaria transmission, but they are given less emphasis in prioritizing malaria prevention interventions. This study was aimed at assessing the ownership of long-lasting insecticide treated bed nets (LLINs), its utilization and factors associated with ownership of LLINs by households and LLINs utilization among SAC in malaria-prone areas of Dara Mallo and Uba Debretsehay districts in Southern Ethiopia, October to December 2019.
Methods: This study is part of a baseline assessment in a cluster-randomized controlled trial. The data was collected through interview and observation, following a structured questionnaire, of 2261 SAC households. Univariable and multivariable multilevel logistic regressions were used to assess the association between LLINs ownership and utilization and potential predictor variables. Odds ratio (OR) and corresponding 95% confidence interval (CI) were used to determine the strength and statistical significance of association.
Results: The ownership of at least one LLIN by households of SAC was about 19.3% (95% CI 17.7-21.0%) but only 10.3% % (95% CI 7.7-13.7%) of these households had adequate access of bed nets to the household members. Ownership of bed net was marginally affected by living in semi-urban area (adjusted OR = 2.6; 95% CI 1.0-6.9) and occupational status of the household head being a civil servant (adjusted OR = 2.7; 95% CI 0.9-7.9). About 7.8% (95% CI 6.7-10.0%) of all SAC participated in the study and 40.4% (95% CI 57.4-66.7%) of children in households owning at least one LLIN passed the previous night under LLIN. LLIN utilization by SAC conditional to presence of at least one net in the household was significantly correlated with education level of mother above grade 6 (adjusted OR = 3.4; 95% CI 1.3-9.3) and the household size to bed net ratio less than or equal to 2 (adjusted OR = 20.7; 95% CI 4.7-132.5).

Conclusion: Ownership of bed net was lower than universal coverage of at least one bed net for two individuals. It is important to monitor replacement needs and educate mothers with low education level with their SAC on the benefit of consistent utilization of bed nets.

Intermittent preventative treatment and seasonal malaria prophylaxis

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Malaria Chemoprevention in the Postdischarge Management of Severe Anemia

Titus K Kwambai[1], Aggrey Dhabangi[1], Richard Idro[1], Robert Opoka[1], Victoria Watson[1], Simon Kariuki[1], Nickline A Kuya[1], Eric D Onyango[1], Kephas Otieno[1], Aaron M Samuels[1], Meghna R Desai[1], Michael Boele van Hensbroek[1], Duolao Wang[1], Chandy C John[1], Bjarne Robberstad[1], Kamija S Phiri[1], Feiko O Ter Kuile[1]

Abstract

Background: Children who have been hospitalized with severe anemia in areas of Africa in which malaria is endemic have a high risk of readmission and death within 6 months after discharge. No prevention strategy specifically addresses this period.

Methods: We conducted a multicenter, two-group, randomized, placebo-controlled trial in nine hospitals in Kenya and Uganda to determine whether 3 months of malaria chemoprevention could reduce morbidity and mortality after hospital discharge in children younger than 5 years of age who had been admitted with severe anemia. All children received standard in-hospital care for severe anemia and a 3-day course of artemether-lumefantrine at discharge. Two weeks after discharge, children were randomly assigned to receive dihydroartemisinin-piperaquine (chemoprevention group) or placebo, administered as 3-day courses at 2, 6, and 10 weeks after discharge. Children were followed for 26 weeks after discharge. The primary outcome was one or more hospital readmissions for any reason or death from the time of randomization to 6 months after discharge. Conditional risk-set modeling for recurrent events was used to calculate hazard ratios with the use of the Prentice-Williams-Peterson total-time approach.

Results: From May 2016 through May 2018, a total of 1049 children underwent randomization; 524 were assigned to the chemoprevention group and 525 to the placebo group. From week 3 through week 26, a total of 184 events of readmission or death occurred in the chemoprevention group and 316 occurred in the placebo group (hazard ratio, 0.65; 95% confidence interval [CI], 0.54 to 0.78; P<0.001). The lower incidence of readmission or death in the chemoprevention group than in the placebo group was restricted to the intervention period (week 3 through week 14) (hazard ratio, 0.30; 95% CI, 0.22 to 0.42) and was not sustained after that time (week 15 through week 26) (hazard ratio, 1.13; 95% CI, 0.87 to 1.47). No serious adverse events were attributed to dihydroartemisinin-piperaquine.

Conclusions: In areas with intense malaria transmission, 3 months of postdischarge malaria chemoprevention with monthly dihydroartemisinin-piperaquine in children who had recently received treatment for severe anemia prevented more deaths or readmissions for any reason after discharge than placebo.

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Evaluation of seasonal malaria chemoprevention in two areas of intense seasonal malaria transmission: Secondary analysis of a household-randomised, placebo-controlled trial in Houndé District, Burkina Faso and Bougouni District, Mali

Matthew E Cairns[1], Issaka Sagara[2], Issaka Zongo[3], Irene Kuepfer[4 5], Ismaila Thera[2], Frederic Nikiema[3], Modibo Diarra[2], Serge R Yerbanga[3], Amadou Barry[2], Amadou Tapily[2], Samba Coumare[2], Paul Milligan[1], Halidou Tinto[3], Jean Bosco Ouédraogo[3], Daniel Chandramohan[5], Brian Greenwood[5], Abdoulaye Djimde[2], Alassane Dicko[2]

Abstract

Background: Seasonal malaria chemoprevention (SMC) is now widely deployed in the Sahel, including several countries that are major contributors to the global burden of malaria. Consequently, it is important to understand whether SMC continues to provide a high level of protection and how SMC might be improved. SMC was evaluated using data from a large, household-randomised trial in Houndé, Burkina Faso and Bougouni, Mali.

Methods and findings: The parent trial evaluated monthly SMC plus either azithromycin (AZ) or placebo, administered as directly observed therapy 4 times per year between August and November (2014-2016). In July 2014, 19,578 children aged 3-59 months were randomised by household to study group. Children who remained within the age range 3-59 months in August each year, plus children born into study households or who moved into the study area, received study drugs in 2015 and 2016. These analyses focus on the approximately 10,000 children (5,000 per country) under observation each year in the SMC plus placebo group. Despite high coverage and high adherence to SMC, the incidence of hospitalisations or deaths due to malaria and uncomplicated clinical malaria remained high in the study areas (overall incidence rates 12.5 [95% confidence interval (CI): 11.2, 14.1] and 871.1 [95% CI: 852.3, 890.6] cases per 1,000 person-years, respectively) and peaked in July each year, before SMC delivery began in August. The incidence rate ratio comparing SMC within the past 28 days with SMC more than 35 days ago-adjusted for age, country, and household clustering-was 0.13 (95% CI: 0.08, 0.20), P < 0.001 for malaria hospitalisations and deaths from malaria and 0.21 (95% CI 0.20, 0.23), P < 0.001 for uncomplicated malaria, indicating protective efficacy of 87.4% (95% CI: 79.6%, 92.2%) and 78.3% (95% CI: 76.8%, 79.6%), respectively. The prevalence of malaria parasitaemia at weekly surveys during the rainy season and at the end of the transmission season was several times higher in children who missed the SMC course preceding the survey contact, and the smallest prevalence ratio observed was 2.98 (95% CI: 1.95, 4.54), P < 0.001. The frequency of molecular markers of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) resistance did not increase markedly over the study period either amongst study children or amongst school-age children resident in the study areas. After 3 years of SMC deployment, the day 28 PCR-unadjusted adequate clinical and parasitological response rate of the SP + AQ regimen in children with asymptomatic malaria was 98.3% (95% CI: 88.6%, 99.8%) in Burkina Faso and 96.1% (95% CI: 91.5%, 98.2%) in Mali. Key limitations of this study are the potential overdiagnosis of uncomplicated malaria by rapid diagnostic tests and the potential for residual confounding from factors related to adherence to the monthly SMC schedule.

Conclusion: Despite strong evidence that SMC is providing a high level of protection, the burden of malaria remains substantial in the 2 study areas. These results emphasise the need for continuing support of SMC programmes. A fifth monthly SMC course is needed to adequately cover the whole transmission season in the study areas and in settings with similar epidemiology.

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Impact of Three-Year Intermittent Preventive Treatment Using Artemisinin-Based Combination Therapies on Malaria Morbidity in Malian Schoolchildren

Hamma Maiga[1 2 3], Breanna Barger[4], Issaka Sagara[2 3], Abdoulaye Guindo[2 3], Oumar B Traore[2 3], Mamadou Tekete[2 3], Antoine Dara[2 3], Zoumana I Traore[2 3], Modibo Diarra[2 3], Samba Coumare[2 3], Aly Kodio[2 3], Ousmane B Toure[2 3], Ogobara K Doumbo[2 3], Abdoulaye A Djimde[2 3]

Abstract

Previous studies have shown that a single season of intermittent preventive treatment in schoolchildren (IPTsc) targeting the transmission season has reduced the rates of clinical malaria, all-cause clinic visits, asymptomatic parasitemia, and anemia. Efficacy over the course of multiple years of IPTsc has been scantly investigated.

Methods: An open, randomized-controlled trial among schoolchildren aged 6-13 years was conducted from September 2007 to January 2010 in Kolle, Mali. Students were included in three arms: sulphadoxine-pyrimethamine+artesunate (SP+AS), amodiaquine+artesunate (AQ+AS), and control (C). All students received two full doses, given 2 months apart, and were compared with respect to the incidence of clinical malaria, all-cause clinic visits, asymptomatic parasitemia, and anemia.

Results: A total of 296 students were randomized. All-cause clinic visits were in the SP+AS versus control (29 (20.1%) vs. 68 (47.2%); 20 (21.7%) vs. 41 (44.6%); and 14 (21.2%) vs. 30 (44.6%); $p < 0.02$) in 2007, 2008, and 2009, respectively. The prevalence of asymptomatic parasitemia was lower in the SP+AS compared to control (38 (7.5%) vs. 143 (28.7%); and 47 (12.7%) vs. 75 (21.2%); $p < 0.002$) in 2007 and 2008, respectively. Hemoglobin concentration was significantly higher in children receiving SP+AS (11.96, 12.06, and 12.62 g/dL) than in control children (11.60, 11.64, and 12.15 g/dL; $p < 0.001$) in 2007, 2008, and 2009, respectively. No impact on clinical malaria was observed.

Conclusion: IPTsc with SP+AS reduced the rates of all-cause clinic visits and anemia during a three-year implementation.

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Adherence to Mass Drug Administration with Dihydroartemisinin-Piperaquine and *Plasmodium falciparum* Clearance in Southern Province, Zambia

Timothy P Finn[1], Travis R Porter[1], Hawela Moonga[2], Kafula Silumbe[3], Rachel F Daniels[4 5], Sarah K Volkman[6 4 5], Joshua O Yukich[1], Joseph Keating[1], Adam Bennett[7], Richard W Steketee[8], John M Miller[3], Thomas P Eisele[1]

Abstract
Mass drug administration (MDA) with artemisinin combination therapy is a potentially useful tool for malaria elimination programs, but its success depends partly on drug effectiveness and treatment coverage in the targeted population. As part of a cluster-randomized controlled trial in Southern Province, Zambia evaluating the impact of MDA and household focal MDA (fMDA) with dihydroartemisinin-piperaquine (DHAp), sub-studies were conducted investigating population drug adherence rates and effectiveness of DHAp as administered in clearing *Plasmodium falciparum* infections following household mass administration. Adherence information was reported for 181,534 of 336,821 DHAp (53.9%) treatments administered during four rounds of MDA/fMDA, of which 153,197 (84.4%) reported completing the full course of DHAp. The proportion of participants fully adhering to the treatment regimen differed by MDA modality (MDA versus fMDA), RDT status, and whether the first dose was observed by those administering treatments. Among a subset of participants receiving DHAp and selected for longitudinal follow-up, 58 were positive for asexual-stage *P. falciparum* infection by microscopy at baseline. None of the 45 participants followed up at days 3 and/or 7 were slide positive for asexual-stage parasitemia. For those with longer term follow-up, one participant was positive 47 days after treatment, and two additional participants were positive after 69 days, although these two were determined to be new infections by genotyping. High completion of a 3-day course of DHAp and parasite clearance in the context of household MDA are promising as Zambia's National Malaria Programme continues to weigh appropriate interventions for malaria elimination.

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Impact of Four Rounds of Mass Drug Administration with Dihydroartemisinin-Piperaquine Implemented in Southern Province, Zambia

Thomas P Eisele[1], Adam Bennett[2], Kafula Silumbe[3], Timothy P Finn[1], Travis R Porter[1], Victor Chalwe[4], Busiku Hamainza[5], Hawela Moonga[5], Emmanuel Kooma[5], Elizabeth Chizema Kawesha[5], Mulakwa Kamuliwo[6], Joshua O Yukich[1], Joseph Keating[1], Kammerle Schneider[7], Ruben O Conner[7], Duncan Earle[3], Laurence Slutsker[7], Richard W Steketee[7], John M Miller[3]

Abstract
Over the past decade, Zambia has made substantial progress against malaria and has recently set the ambitious goal of eliminating by 2021. In the context of very high vector control and improved access to malaria diagnosis and treatment in Southern Province, we implemented a community-randomized controlled trial to assess the impact of four rounds of community-wide mass drug administration (MDA) and household-level MDA (focal MDA) with dihydroartemisinin-piperaquine (DHAP) implemented between December 2014 and February 2016. The mass treatment campaigns achieved relatively good household coverage (63-79%), were widely accepted by the community (ranging from 87% to 94%), and achieved very high adherence to the DHAP regimen (81-96%). Significant declines in all malaria study end points were observed, irrespective of the exposure group, with the overall parasite prevalence during the peak transmission season declining by 87.2% from 31.3% at baseline to 4.0% in 2016 at the end of the trial. Children in areas of lower transmission (< 10% prevalence at baseline) that received four MDA rounds had a 72% (95% CI = 12-91%)

reduction in malaria parasite prevalence as compared with those with the standard of care without any mass treatment. Mass drug administration consistently had the largest short-term effect size across study end points in areas of lower transmission following the first two MDA rounds. In the context of achieving very high vector control coverage and improved access to diagnosis and treatment for malaria, our results suggest that MDA should be considered for implementation in African settings for rapidly reducing malaria outcomes in lower transmission settings.

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A Longitudinal Cohort to Monitor Malaria Infection Incidence during Mass Drug Administration in Southern Province, Zambia

Adam Bennett[1], Travis R Porter[2], Mulenga C Mwenda[3], Joshua O Yukich[2], Timothy P Finn[2], Chris Lungu[3], Kafula Silumbe[3], Brenda Mambwe[3], Sandra Chishimba[3], Conceptor Mulube[3], Daniel J Bridges[3], Busiku Hamainza[4], Laurence Slutsker[5], Richard W Steketee[5], John M Miller[3], Thomas P Eisele[2]

Abstract

Rigorous evidence of effectiveness is needed to determine where and when to apply mass drug administration (MDA) or focal MDA (fMDA) as part of a malaria elimination strategy. The Zambia National Malaria Elimination Centre recently completed a community-randomized controlled trial in Southern Province to evaluate MDA and fMDA for transmission reduction. To assess the role of MDA and fMDA on infection incidence, we enrolled a longitudinal cohort for an 18-month period of data collection including monthly malaria parasite infection detection based on polymerase chain reaction and compared time to first infection and cumulative infection incidence outcomes across study arms using Cox proportional hazards and negative binomial models. A total of 2,026 individuals from 733 households were enrolled and completed sufficient follow-up for inclusion in analysis. Infection incidence declined dramatically across all study arms during the period of study, and MDA was associated with reduced risk of first infection (hazards ratio: 0.36; 95% CI: 0.16-0.80) and cumulative infection incidence during the first rainy season (first 5 months of follow-up) (incidence rate ratio: 0.34; 95% CI: 0.12-0.95). No significant effect was found for fMDA or for either arm over the full study period. Polymerase chain reaction infection status at baseline was strongly associated with follow-up infection. The short-term effects of MDA suggest it may be an impactful accelerator of transmission reduction in areas with high coverage of case management and vector control and should be considered as part of a malaria elimination strategy.

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Assessment of the Acceptability of Testing and Treatment during a Mass Drug Administration Trial for Malaria in Zambia Using Mixed Methods

Kafula Silumbe[1], Timothy P Finn[2], Todd Jennings[1], Chilumba Sikombe[1], Elizabeth Chiyende[1], Busiku Hamainza[3], Elizabeth Chizema Kawesha[3], Thomas P Eisele[2], Duncan Earle[1], Richard W Steketee[1], John M Miller[1]

Abstract

From 2014 to 2016, a community-randomized controlled trial in Southern Province, Zambia, compared mass drug administration (MDA) and focal MDA (fMDA) with the standard of care. Acceptability of the intervention was assessed quantitatively using closed-ended and Likert scale-based questions posed during three household surveys conducted from April to May in 2014, 2015, and 2016 in 40 health catchments that implemented MDA and fMDA and 20 catchments that served as trial controls. In 2014 and 2015, 47 households per catchment were selected, targeting 1,880 households in MDA and fMDA trial arms; in 2016, 55 households per catchment were selected for a target of 2,200 households in MDA and fMDA trial arms. Concurrently, 27 focus group discussions and 23 in-depth interviews with 248 participants were conducted on reasons for testing and treatment refusal, reasons for nonadherence, and community perception of the MDA campaign. Results demonstrated that the MDA campaign was highly accepted with more than 99% of respondents stating that they would take treatment if positive for malaria. High acceptability at baseline could be associated with test-and-treat campaigns recently conducted in the study area. There was a large increase in the acceptability of prophylactic treatment if negative for malaria from the baseline to follow-up survey for adults and children, from 62% to 96% for each. This likely resulted from an intensive community-wide sensitization program that occurred before the first treatment round at each household during community health worker visits.

Environmental preventative strategies for malaria

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doi: 10.1016/S2542-5196(21)00002-4.

Improved housing versus usual practice for additional protection against clinical malaria in The Gambia (RooPfs): a household-randomised controlled trial

Margaret Pinder[1], John Bradley[2], Musa Jawara[3], Muna Affara[4], Lesong Conteh[5], Simon Correa[3], David Jeffries[3], Caroline Jones[6], Balla Kandeh[7], Jakob Knudsen[8], Yekini Olatunji[3], Elisa Sicuri[9], Umberto D'Alessandro[10], Steve W Lindsay[11]

Abstract

Background: In malaria-endemic areas, residents of modern houses have less malaria than those living in traditional houses. We aimed to assess whether children in The Gambia received an incremental benefit from improved housing, where current best practice of insecticide-treated nets, indoor residual spraying, seasonal malaria chemoprevention in children younger than 5 years, and prompt treatment against clinical malaria was in place.

Methods: In this randomised controlled study, 800 households with traditional thatched-roofed houses were randomly selected from 91 villages in the Upper River Region of The Gambia. Within each village, equal numbers of houses were randomly allocated to the control and intervention groups using a sampling frame. Houses in the intervention group were modified with metal roofs and screened doors and windows, whereas houses in the

control group received no modifications. In each group, clinical malaria in children aged 6 months to 13 years was monitored by active case detection over 2 years (2016-17). We did monthly collections from indoor light traps to estimate vector densities. Primary endpoints were the incidence of clinical malaria in study children with more than 50% of observations each year and household vector density. The trial is registered at ISRCTN02622179.
Findings: In June, 2016, 785 houses had one child each recruited into the study (398 in unmodified houses and 402 in modified houses). 26 children in unmodified houses and 28 children in modified houses did not have at least 50% of visits in a year and so were excluded from analysis. 38 children in unmodified houses were recruited after study commencement, as were 21 children in modified houses, meaning 410 children in unmodified houses and 395 in modified houses were included in the parasitological analyses. At the end of the study, 659 (94%) of 702 children were reported to have slept under an insecticide-treated net; 662 (88%) of 755 children lived in houses that received indoor residual spraying; and 151 (90%) of 168 children younger than 5 years had seasonal malaria chemoprevention. Incidence of clinical malaria was 0·12 episodes per child-year in children in the unmodified houses and 0·20 episodes per child-year in the modified houses (unadjusted incidence rate ratio [RR] 1·68 [95% CI 1·11-2·55], p=0·014). Household vector density was 3·30 Anopheles gambiae per house per night in the unmodified houses compared with 3·60 in modified houses (unadjusted RR 1·28 [0·87-1·89], p=0·21).
Interpretation: Improved housing did not provide protection against clinical malaria in this area of low seasonal transmission with high coverage of insecticide-treated nets, indoor residual spraying, and seasonal malaria chemoprevention.

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Evaluation of the effectiveness of topical repellent distributed by village health volunteer networks against Plasmodium spp. infection in Myanmar: A stepped-wedge cluster randomised trial

Paul A Agius[1,2], Julia C Cutts[1], Win Han Oo[1], Aung Thi[3], Katherine O'Flaherty[1,4], Kyaw Zayar Aung[1], Htin Kyaw Thu[1], Poe Poe Aung[1], Myat Mon Thein[1], Nyi Nyi Zaw[1], Wai Yan Min Htay[1], Aung Paing Soe[1], Zahra Razook[5], Alyssa E Barry[1,5,6], Win Htike[1], Angela Devine[4,7], Julie A Simpson[4], Brendan S Crabb[1], James G Beeson[1,8,9], Naanki Pasricha[1], Freya J I Fowkes[1,2,4]

Abstract
Background: The World Health Organization has yet to endorse deployment of topical repellents for malaria prevention as part of public health campaigns. We aimed to quantify the effectiveness of repellent distributed by the village health volunteer (VHV) network in the Greater Mekong Subregion (GMS) in reducing malaria in order to advance regional malaria elimination.
Methods and findings: Between April 2015 and June 2016, a 15-month stepped-wedge cluster randomised trial was conducted in 116 villages in Myanmar (stepped monthly in blocks) to test the effectiveness of 12% N,N-diethylbenzamide w/w cream distributed by VHVs, on Plasmodium spp. infection. The median age of participants was 18 years, approximately half were female, and the majority were either village residents (46%) or forest dwellers (40%). No adverse events were reported during the study. Generalised linear

mixed modelling estimated the effect of repellent on infection detected by rapid diagnostic test (RDT) (primary outcome) and polymerase chain reaction (PCR) (secondary outcome). Overall Plasmodium infection detected by RDT was low (0.16%; 50/32,194), but infection detected by PCR was higher (3%; 419/13,157). There was no significant protection against RDT-detectable infection (adjusted odds ratio [AOR] = 0.25, 95% CI 0.004-15.2, p = 0.512). In Plasmodium-species-specific analyses, repellent protected against PCR-detectable P. falciparum (adjusted relative risk ratio [ARRR] = 0.67, 95% CI 0.47-0.95, p = 0.026), but not P. vivax infection (ARRR = 1.41, 95% CI 0.80-2.47, p = 0.233). Repellent effects were similar when delayed effects were modelled, across risk groups, and regardless of village-level and temporal heterogeneity in malaria prevalence. The incremental cost-effectiveness ratio was US$256 per PCR-detectable infection averted. Study limitations were a lower than expected Plasmodium spp. infection rate and potential geographic dilution of the intervention.
Conclusions: In this study, we observed apparent protection against new infections associated with the large-scale distribution of repellent by VHVs. Incorporation of repellent into national strategies, particularly in areas where bed nets are less effective, may contribute to the interruption of malaria transmission. Further studies are warranted across different transmission settings and populations, from the GMS and beyond, to inform WHO public health policy on the deployment of topical repellents for malaria prevention.

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House modifications for preventing malaria

Joanna Furnival-Adams[1], Evelyn A Olanga[2], Mark Napier[3 4], Paul Garner[1]

Furnival-Adams J, Olanga EA, Napier M, Garner P.Cochrane Database Syst Rev. 2021 Jan 20;1:CD013398.doi: 10.1002/14651858.CD013398.pub3.PMID: 33471371

Abstract

Background: Despite being preventable, malaria remains an important public health problem. The World Health Organization (WHO) reports that overall progress in malaria control has plateaued for the first time since the turn of the century. Researchers and policymakers are therefore exploring alternative and supplementary malaria vector control tools. Research in 1900 indicated that modification of houses may be effective in reducing malaria: this is now being revisited, with new research now examining blocking house mosquito entry points or modifying house construction materials to reduce exposure of inhabitants to infectious bites.
Objectives: To assess the effects of house modifications on malaria disease and transmission.
Search methods: We searched the Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); Centre for Agriculture and Bioscience International (CAB) Abstracts (Web of Science); and the Latin American and Caribbean Health Science Information database (LILACS), up to 1 November 2019. We also searched the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), ClinicalTrials.gov (www.clinicaltrials.gov), and the ISRCTN registry (www.isrctn.com/) to identify ongoing trials up to the same date.

Selection criteria: Randomized controlled trials, including cluster-randomized controlled trials (cRCTs), cross-over studies, and stepped-wedge designs were eligible, as were quasi-experimental trials, including controlled before-and-after studies, controlled interrupted time series, and non-randomized cross-over studies. We only considered studies reporting epidemiological outcomes (malaria case incidence, malaria infection incidence or parasite prevalence). We also summarised qualitative studies conducted alongside included studies.
Data collection and analysis: Two review authors selected eligible studies, extracted data, and assessed the risk of bias. We used risk ratios (RR) to compare the effect of the intervention with the control for dichotomous data. For continuous data, we presented the mean difference; and for count and rate data, we used rate ratios. We presented all results with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach.
Main results: Six cRCTs met our inclusion criteria, all conducted in sub-Saharan Africa; three randomized by household, two by village, and one at the community level. All trials assessed screening of windows, doors, eaves, ceilings or any combination of these; this was either alone, or in combination with eave closure, roof modification or eave tube installation (a "lure and kill" device that reduces mosquito entry whilst maintaining some airflow). In two trials, the interventions were insecticide-based. In five trials, the researchers implemented the interventions. The community implemented the interventions in the sixth trial. At the time of writing the review, two of the six trials had published results, both of which compared screened houses (without insecticide) to unscreened houses. One trial in Ethiopia assessed screening of windows and doors. Another trial in the Gambia assessed full screening (screening of eaves, doors and windows), as well as screening of ceilings only. Screening may reduce clinical malaria incidence caused by Plasmodium falciparum (rate ratio 0.38, 95% CI 0.18 to 0.82; 1 trial, 184 participants, 219.3 person-years; low-certainty evidence; Ethiopian study). For malaria parasite prevalence, the point estimate, derived from The Gambia study, was smaller (RR 0.84, 95% CI 0.60 to 1.17; 713 participants, 1 trial; moderate-certainty evidence), and showed an effect on anaemia (RR 0.61, 95% CI 0.42, 0.89; 705 participants; 1 trial, moderate-certainty evidence). Screening may reduce the entomological inoculation rate (EIR): both trials showed lower estimates in the intervention arm. In the Gambian trial, there was a mean difference in EIR between the control houses and treatment houses ranging from 0.45 to 1.50 (CIs ranged from -0.46 to 2.41; low-certainty evidence), depending on the study year and treatment arm. The Ethiopian trial reported a mean difference in EIR of 4.57, favouring screening (95% CI 3.81 to 5.33; low-certainty evidence). Pooled analysis of the trials showed that individuals living in fully screened houses were slightly less likely to sleep under a bed net (RR 0.84, 95% CI 0.65 to 1.09; 2 trials, 203 participants). In one trial, bed net usage was also lower in individuals living in houses with screened ceilings (RR 0.69, 95% CI 0.50 to 0.95; 1 trial, 135 participants).
Authors' conclusions: Based on the two trials published to date, there is some evidence that screening may reduce malaria transmission and malaria infection in people living in the house. The four trials awaiting publication are likely to enrich the current evidence base, and we will add these to this review when they become available.

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Reduced exposure to malaria vectors following indoor residual spraying of pirimiphos-methyl in a high-burden district of rural Mozambique with high ownership of long-lasting insecticidal nets: entomological surveillance results from a cluster-randomized trial

Joseph M Wagman[1], Kenyssony Varela[2], Rose Zulliger[3], Abuchahama Saifodine[4], Rodaly Muthoni[2], Stephen Magesa[2], Carlos Chaccour[5,6], Christelle Gogue[7], Kenzie Tynuv[7], Aklilu Seyoum[8], Dereje Dengela[8], Francisco Saúte[5], Jason H Richardson[9], Christen Fornadel[9], Yvonne-Marie Linton[10,11], Laurence Slutsker[7], Baltazar Candrinho[12], Molly Robertson[7]

Abstract

Background: The need to develop new products and novel approaches for malaria vector control is recognized as a global health priority. One approach to meeting this need has been the development of new products for indoor residual spraying (IRS) with novel active ingredients for public health. While initial results showing the impact of several of these next-generation IRS products have been encouraging, questions remain about how to best deploy them for maximum impact. To help address these questions, a 2-year cluster-randomized controlled trial to measure the impact of IRS with a microencapsulated formulation of pirimiphos-methyl (PM) in an area with high ownership of long-lasting insecticidal nets (LLINs) was conducted in a high-transmission district of central Mozambique with pyrethroid resistant vectors. Presented here are the results of the vector surveillance component of the trial.

Methods: The 2 year, two-armed trial was conducted in Mopeia District, Zambezia Province, Mozambique. In ten sentinel villages, five that received IRS with PM in October-November 2016 and again in October-November 2017 and five that received no IRS, indoor light trap collections and paired indoor-outdoor human landing collections catches (HLCs) were conducted monthly from September 2016 through October 2018. A universal coverage campaign in June 2017, just prior to the second spray round, distributed 131,540 standard alpha-cypermethrin LLINs across all study villages and increased overall net usage rates in children under 5 years old to over 90%.

Results: The primary malaria vector during the trial was Anopheles funestus sensu lato (s.l.), and standard World Health Organization (WHO) tube tests with this population indicated variable but increasing resistance to pyrethroids (including alpha-cypermethrin, from > 85% mortality in 2017 to 7% mortality in 2018) and uniform susceptibility to PM (100% mortality in both years). Over the entire duration of the study, IRS reduced An. funestus s.l. densities by 48% (CI_{95} 33-59%; $p < 0.001$) in indoor light traps and by 74% (CI_{95} 38-90%; $p = 0.010$) during indoor and outdoor HLC, though in each study year reductions in vector density were consistently greatest in those months immediately following the IRS campaigns and waned over time. Overall there was no strong preference for An. funestus to feed indoors or outdoors, and these biting behaviours did not differ significantly across study arms: observed indoor-outdoor biting ratios were 1.10 (CI_{95} 1.00-1.21) in no-IRS villages and 0.88 (CI_{95} 0.67-1.15) in IRS villages. The impact of IRS was consistent in reducing HLC exposures both indoors (75% reduction: CI_{95} 47-88%; $p = 0. < 0.001$) and outdoors (68% reduction: CI_{95} 22-87%; $p = 0.012$). While substantially fewer Anopheles gambiae s.l. were collected during the study, trends show a similar impact of IRS on this key vector group as well, with a 33% (CI_{95} 7-53%; $p = 0.019$) reduction in mosquitoes collected in light traps and a non-statistically significant 39% reduction ($p = 0.249$) in HLC landing rates.

Conclusion: IRS with PM used in addition to pyrethroid-only LLINs substantially reduced human exposures to malaria vectors during both years of the cluster-randomized controlled trial in Mopeia-a high-burden district where the primary vector, An. funestus s.l., was equally likely to feed indoors or outdoors and demonstrated increasing resistance to pyrethroids. Findings suggest that IRS with PM can provide effective vector control, including in some settings where pyrethroid-only ITNs are widely used.

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Impact and cost-effectiveness of a lethal house lure against malaria transmission in central Côte d'Ivoire: a two-arm, cluster-randomised controlled trial

Eleanore D Sternberg[1], Jackie Cook[2], Ludovic P Ahoua Alou[3], Serge Brice Assi[3], Alphonsine A Koffi[3], Dimi T Doudou[4], Carine J Aoura[3], Rosine Z Wolie[5], Welbeck A Oumbouke[6], Eve Worrall[7], Immo Kleinschmidt[8], Raphael N'Guessan[9], Matthew B Thomas[10]

Abstract

Background: New vector control tools are required to sustain the fight against malaria. Lethal house lures, which target mosquitoes as they attempt to enter houses to blood feed, are one approach. Here we evaluated lethal house lures consisting of In2Care (Wageningen, Netherlands) Eave Tubes, which provide point-source insecticide treatments against host-seeking mosquitoes, in combination with house screening, which aims to reduce mosquito entry.

Methods: We did a two-arm, cluster-randomised controlled trial with 40 village-level clusters in central Côte d'Ivoire between Sept 26, 2016, and April 10, 2019. All households received new insecticide-treated nets at universal coverage (one bednet per two people). Suitable households within the clusters assigned to the treatment group were offered screening plus Eave Tubes, with Eave Tubes treated using a 10% wettable powder formulation of the pyrethroid β-cyfluthrin. Because of the nature of the intervention, treatment could not be masked for households and field teams, but all analyses were blinded. The primary endpoint was clinical malaria incidence recorded by active case detection over 2 years in cohorts of children aged 6 months to 10 years. This trial is registered with ISRCTN, ISRCTN18145556.

Findings: 3022 houses received screening plus Eave Tubes, with an average coverage of 70% across the intervention clusters. 1300 eligible children were recruited for active case detection in the control group and 1260 in the intervention group. During the 2-year follow-up period, malaria case incidence was 2·29 per child-year (95% CI 1·97-2·61) in the control group and 1·43 per child-year (1·21-1·65) in the intervention group (hazard ratio 0·62, 95% CI 0·51-0·76; p<0·0001). Cost-effectiveness simulations suggested that screening plus Eave Tubes has a 74·0% chance of representing a cost-effective intervention, compared with existing healthcare activities in Côte d'Ivoire, and is similarly cost-effective to other core vector control interventions across sub-Saharan Africa. No serious adverse events associated with the intervention were reported during follow-up.

Interpretation: Screening plus Eave Tubes can provide protection against malaria in addition to the effects of insecticide-treated nets, offering potential for a new, cost-effective strategy to supplement existing vector control tools. Additional trials are needed to confirm these initial results and further optimise Eave Tubes and the lethal house lure concept to facilitate adoption.

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House modifications for preventing malaria

Joanna Furnival-Adams[1], Evelyn A Olanga[2], Mark Napier[3 4], Paul Garner[1]

Abstract

Background: Despite being preventable, malaria remains an important public health problem. The World Health Organization (WHO) reports that overall progress in malaria control has plateaued for the first time since the turn of the century. Researchers and policymakers are therefore exploring alternative and supplementary malaria vector control tools. Research in 1900 indicated that modification of houses may be effective in reducing malaria: this is now being revisited, with new research now examining blocking house mosquito entry points or modifying house construction materials to reduce exposure of inhabitants to infectious bites.

Objectives: To assess the effects of house modifications on malaria disease and transmission.

Search methods: We searched the Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); Centre for Agriculture and Bioscience International (CAB) Abstracts (Web of Science); and the Latin American and Caribbean Health Science Information database (LILACS), up to 1 November 2019. We also searched the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), ClinicalTrials.gov (www.clinicaltrials.gov), and the ISRCTN registry (www.isrctn.com/) to identify ongoing trials up to the same date.

Selection criteria: Randomized controlled trials, including cluster-randomized controlled trials (cRCTs), cross-over studies, and stepped-wedge designs were eligible, as were quasi-experimental trials, including controlled before-and-after studies, controlled interrupted time series, and non-randomized cross-over studies. We only considered studies reporting epidemiological outcomes (malaria case incidence, malaria infection incidence or parasite prevalence). We also summarised qualitative studies conducted alongside included studies.

Data collection and analysis: Two review authors selected eligible studies, extracted data, and assessed the risk of bias. We used risk ratios (RR) to compare the effect of the intervention with the control for dichotomous data. For continuous data, we presented the mean difference; and for count and rate data, we used rate ratios. We presented all results with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach.

Main results: Six cRCTs met our inclusion criteria, all conducted in sub-Saharan Africa; three randomized by household, two by village, and one at the community level. All trials assessed screening of windows, doors, eaves, ceilings or any combination of these; this was either alone, or in combination with eave closure, roof modification or eave tube installation (a "lure and kill" device that reduces mosquito entry whilst maintaining some airflow). In two trials, the interventions were insecticide-based. In five trials, the researchers implemented the interventions. The community implemented the interventions in the sixth trial. At the time of writing the review, two of the six trials had published results, both of which compared screened houses (without insecticide) to unscreened houses. One trial in Ethiopia assessed screening of windows and doors. Another trial in the Gambia assessed full screening (screening of eaves, doors and windows), as well as screening of ceilings only.

Screening may reduce clinical malaria incidence caused by Plasmodium falciparum (rate ratio 0.38, 95% CI 0.18 to 0.82; 1 trial, 184 participants, 219.3 person-years; low-certainty evidence; Ethiopian study). For malaria parasite prevalence, the point estimate, derived from The Gambia study, was smaller (RR 0.84, 95% CI 0.60 to 1.17; 713 participants, 1 trial; low-certainty evidence), and showed an effect on anaemia (RR 0.61, 95% CI 0.42, 0.89; 705 participants; 1 trial, moderate-certainty evidence). Screening may reduce the entomological inoculation rate (EIR): both trials showed lower estimates in the intervention arm. In the Gambian trial, there was a mean difference in EIR between the control houses and treatment houses ranging from 0.45 to 1.50 (CIs ranged from -0.46 to 2.41; low-certainty evidence), depending on the study year and treatment arm. The Ethiopian trial reported a mean difference in EIR of 4.57, favouring screening (95% CI 3.81 to 5.33; low-certainty evidence). Pooled analysis of the trials showed that individuals living in fully screened houses were slightly less likely to sleep under a bed net (RR 0.84, 95% CI 0.65 to 1.09; 2 trials, 203 participants). In one trial, bed net usage was also lower in individuals living in houses with screened ceilings (RR 0.69, 95% CI 0.50 to 0.95; 1 trial, 135 participants).
Authors' conclusions: Based on the two trials published to date, there is some evidence that screening may reduce malaria transmission and malaria infection in people living in the house. The four trials awaiting publication are likely to enrich the current evidence base, and we will add these to this review when they become available.

Malar J. 2020 Nov 3;19(1):390.
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Evaluating the impact of larviciding with Bti and community education and mobilization as supplementary integrated vector management interventions for malaria control in Kenya and Ethiopia
Clifford M Mutero[1 2], Collins Okoyo[3], Melaku Girma[4], Joseph Mwangangi[5], Lydia Kibe[5], Peter Ng'ang'a[6], Dereje Kussa[7], Gracious Diiro[6], Hippolyte Affognon[8], Charles M Mbogo[3 5]
Abstract
Background: Malaria prevention in Africa is mainly through the use of long-lasting insecticide treated nets (LLINs). The objective of the study was to assess the effect of supplementing LLINs with either larviciding with Bacillus thuringiensis israelensis (Bti) or community education and mobilization (CEM), or with both interventions in the context of integrated vector management (IVM).
Methods: The study involved a factorial, cluster-randomized, controlled trial conducted in Malindi and Nyabondo sites in Kenya and Tolay site in Ethiopia, to assess the impact of the following four intervention options on mosquitoes and malaria prevalence: LLINs only (arm 1); LLINs and Bti (arm 2); LLINs and CEM (arm 3); and, LLINs combined with Bti and CEM (arm 4). Between January 2013 and December 2015, CDC light traps were used to sample adult mosquitoes during the second, third and fourth quarter of each year in 10 houses in each of 16 villages at each of the three study sites. Larvae were sampled once a fortnight from potential mosquito-breeding habitats using standard plastic dippers. Cross-sectional malaria parasite prevalence surveys were conducted involving a total of 11,846 primary school children during the 3-year period, including 4800 children in Tolay, 3000 in Malindi and 4046 in Nyabondo study sites.

Results: Baseline relative indoor anopheline density was 0.11, 0.05 and 0.02 mosquitoes per house per night in Malindi, Tolay and Nyabondo sites, respectively. Nyabondo had the highest recorded overall average malaria prevalence among school children at 32.4%, followed by Malindi with 5.7% and Tolay 1.7%. There was no significant reduction in adult anopheline density at each of the three sites, which could be attributed to adding of the supplementary interventions to the usage of LLINs. Malaria prevalence was significantly reduced by 50% in Tolay when using LLINs coupled with application of Bti, community education and mobilization. The two other sites did not reveal significant reduction of prevalence as a result of combining LLINs with any of the other supplementary interventions.
Conclusion: Combining LLINs with larviciding with Bti and CEM further reduced malaria infection in a low prevalence setting in Ethiopia, but not at sites with relatively higher prevalence in Kenya. More research is necessary at the selected sites in Kenya to periodically determine the suite of vector control interventions and broader disease management strategies, which when integrated would further reduce adult anopheline populations and malaria prevalence beyond what is achieved with LLINs.

Treatment of uncomplicated malaria

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Efficacy and safety of dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Ugandan children: a systematic review and meta-analysis of randomized control trials
Dawit Getachew Assefa[1,2], Eden Dagnachew Zeleke[3,4], Delayehu Bekele[3,5], Hanna Amanuel Tesfahunei[3,6], Emnet Getachew[3,7], Michele Joseph[3], Tsegahun Manyazewal[3]
Abstract
Background: The emergence of artemisinin resistance in Southeast Asia and Plasmodium falciparum kelch13 propeller gene mutations in sub-Saharan African pose the greatest threat to global efforts to control malaria. This is a critical concern in Uganda, where artemisinin-based combination therapy (ACT) is the first-line treatment for uncomplicated falciparum. The objective of this study was to compare the efficacy and safety of dihydroartemisinin-piperaquine (DHA-PQ) and artemether-lumefantrine (AL) for the treatment of uncomplicated falciparum malaria in Ugandan children.
Methods: A search of PubMed and the Cochrane Central Register of Controlled Trials for retrieving randomized controlled trials comparing the efficacy and safety of DHA-PQ and AL for treatment of uncomplicated falciparum malaria in Ugandan children was done. The search was performed up to 31 August 2020. The data extracted from eligible studies and pooled as risk ratio (RR) with a 95% confidence interval (CI), using Rev Man Software (5.4). The protocol was registered in PROSPERO, ID: CRD42020182354.
Results: Eleven trials were included in this review and two of them only included under safety outcome. Total 3798 participants were enrolled. The PCR unadjusted treatment failure was significantly lower with DHA-PQ at day 28 (RR 0.30, 95% CI 0.19-0.49; participants = 7863; studies = 5; I^2 = 93%, low quality evidence) and at day 42 (RR 0.53, 95% CI 0.38-0.76; participants = 1618; studies = 4; I^2 = 79%, moderate quality of evidence). The PCR adjusted

treatment failure at day 42 was significantly lower with DHA-PQ treatment group (RR 0.45, 95% CI 0.28 to 0.72; participants = 1370; studies = 5, high quality of evidence), and it was below 5% in both arms at day 28 (moderate quality of evidence). AL showed a longer prophylactic effect on new infections which may last for up to 63 days (PCR-adjusted treatment failure: RR 2.04, 95% CI 1.13-3.70; participants = 1311; studies = 2, moderate quality of evidence). Compared to AL, DHA-PQ was associated with a slightly higher frequency of cough (RR 1.07, 95% CI 1.01 to 1.13; 2575 participants; six studies; high quality of evidence). In both treatment groups, the risk of recurrent parasitaemia due to possible recrudescence was less than 5% at day 28. The appearance of gametocyte between 29 and 42 days was also significantly lower in DHA-PQ than AL (RR 0.26, 95% CI 0.12 to 0.56; participants = 623; studies = 2; I^2 = 0%).
Conclusion: Compared to AL, DHA-PQ appeared to reduce treatment failure and gametocyte carriage in Ugandan children. This may trigger DHA-PQ to become the first-line treatment option. Both treatments were safe and well-tolerated.

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doi: 10.1002/14651858.CD004529.pub3.
Atovaquone-proguanil for treating uncomplicated Plasmodium falciparum malaria
Andrew Blanshard[1], Paul Hine[2]
Abstract
Background: The World Health Organization (WHO) in 2015 stated atovaquone-proguanil can be used in travellers, and is an option in malaria-endemic areas in combination with artesunate, as an alternative treatment where first-line artemisinin-based combination therapy (ACT) is not available or effective. This review is an update of a Cochrane Review undertaken in 2005.
Objectives: To assess the efficacy and safety of atovaquone-proguanil (alone and in combination with artemisinin drugs) versus other antimalarial drugs for treating uncomplicated Plasmodium falciparum malaria in adults and children.
Search methods: The date of the last trial search was 30 January 2020. Search locations for published trials included the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, and LILACS. To include recently published and unpublished trials, we also searched ClinicalTrials.gov, the metaRegister of Controlled Trials and the WHO International Clinical Trials Registry Platform Search Portal.
Selection criteria: Randomized controlled trials (RCTs) reporting efficacy and safety data for atovaquone-proguanil or atovaquone-proguanil with a partner drug compared with at least one other antimalarial drug for treating uncomplicated Plasmodium falciparum infection.
Data collection and analysis: For this update, two review authors re-extracted data and assessed certainty of evidence. We meta-analyzed data to calculate risk ratios (RRs) with 95% confidence intervals (CI) for treatment failures between comparisons, and for safety outcomes between and across comparisons. Outcome measures include unadjusted treatment failures and polymerase chain reaction (PCR)-adjusted treatment failures. PCR adjustment differentiates new infection from recrudescent infection.
Main results: Seventeen RCTs met our inclusion criteria providing 4763 adults and children from Africa, South-America, and South-East Asia. Eight trials reported PCR-adjusted data to distinguish between new and recrudescent infection during the follow-up period. In this abstract, we report only the comparisons against the three WHO-recommended

antimalarials which were included within these trials. There were two comparisons with artemether-lumefantrine, one trial from 2008 in Ethiopia with 60 participants had two failures with atovaquone-proguanil compared to none with artemether-lumefantrine (PCR-adjusted treatment failures at day 28). A second trial from 2012 in Colombia with 208 participants had one failure in each arm (PCR-adjusted treatment failures at day 42). There was only one comparison with artesunate-amodiaquine from a 2014 trial conducted in Cameroon. There were six failures with atovaquone-proguanil at day 28 and two with artesunate-amodiaquine (PCR-adjusted treatment failures at day 28: 9.4% with atovaquone-proguanil compared to 2.9% with artesunate-amodiaquine; RR 3.19, 95% CI 0.67 to 15.22; 1 RCT, 132 participants; low-certainty evidence), although there was a similar number of PCR-unadjusted treatment failures (9 (14.1%) with atovaquone-proguanil and 8 (11.8%) with artesunate-amodiaquine; RR 1.20, 95% CI 0.49 to 2.91; 1 RCT, 132 participants; low-certainty evidence). There were two comparisons with artesunate-mefloquine from a 2012 trial in Colombia and a 2002 trial in Thailand where there are high levels of multi-resistant malaria. There were similar numbers of PCR-adjusted treatment failures between groups at day 42 (2.7% with atovaquone-proguanil compared to 2.4% with artesunate-mefloquine; RR 1.15, 95% CI 0.57 to 2.34; 2 RCTs, 1168 participants; high-certainty evidence). There were also similar PCR-unadjusted treatment failures between groups (5.3% with atovaquone-proguanil compared to 6.6% with artesunate-mefloquine; RR 0.8, 95% CI 0.5 to 1.3; 1 RCT, 1063 participants; low-certainty evidence). When atovaquone-proguanil was combined with artesunate, there were fewer treatment failures with and without PCR-adjustment at day 28 (PCR-adjusted treatment failures at day 28: 2.16% with atovaquone-proguanil compared to no failures with artesunate-atovaquone-proguanil; RR 5.14, 95% CI 0.61 to 43.52; 2 RCTs, 375 participants, low-certainty evidence) and day 42 (PCR-adjusted treatment failures at day 42: 3.82% with atovaquone-proguanil compared to 2.05% with artesunate-atovaquone-proguanil (RR 1.84, 95% CI 0.95 to 3.56; 2 RCTs, 1258 participants, moderate-certainty evidence). In the 2002 trial in Thailand, there were fewer treatment failures in the artesunate-atovaquone-proguanil group compared to the atovaquone-proguanil group at day 42 with PCR-adjustment. Whilst there were some small differences in which adverse events were more frequent in the atovaquone-proguanil groups compared to comparator drugs, there were no recurrent associations to suggest that atovaquone-proguanil is strongly associated with any specific adverse event.

Authors' conclusions: Atovaquone-proguanil was effective against uncomplicated P falciparum malaria, although in some instances treatment failure rates were between 5% and 10%. The addition of artesunate to atovaquone-proguanil may reduce treatment failure rates. Artesunate-atovaquone-proguanil and the development of parasite resistance may represent an area for further research.

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The risk of Plasmodium vivax parasitaemia after P. falciparum malaria: An individual patient data meta-analysis from the WorldWide Antimalarial Resistance Network

Mohammad S Hossain[1 2 3 4], Robert J Commons[1 2 5], Nicholas M Douglas[2 3], Kamala Thriemer[2], Bereket H Alemayehu[6], Chanaki Amaratunga[7], Anupkumar R Anvikar[8], Elizabeth A

Ashley[9,10], Puji B S Asih[11], Verena I Carrara[9,12], Chanthap Lon[13,14], Umberto D'Alessandro[15], Timothy M E Davis[16], Arjen M Dondorp[9,17], Michael D Edstein[18], Rick M Fairhurst[7], Marcelo U Ferreira[19], Jimee Hwang[20,21], Bart Janssens[22], Harin Karunajeewa[23,24], Jean R Kiechel[25], Simone Ladeia-Andrade[26,27], Moses Laman[16,28], Mayfong Mayxay[9,10,29], Rose McGready[9,12], Brioni R Moore[16,30], Ivo Mueller[31,32,33], Paul N Newton[9,10,17], Nguyen T Thuy-Nhien[34], Harald Noedl[35], Francois Nosten[9,12], Aung P Phyo[12,36], Jeanne R Poespoprodjo[37,38,39], David L Saunders[40], Frank Smithuis[9,36,41], Michele D Spring[13], Kasia Stepniewska[1,9], Seila Suon[42], Yupin Suputtamongkol[43], Din Syafruddin[11,44], Hien T Tran[9,34], Neena Valecha[8], Michel Van Herp[22], Michele Van Vugt[12,17,45], Nicholas J White[9,17], Philippe J Guerin[1,9], Julie A Simpson[1,3], Ric N Price[1,2,9,17]

Abstract

Background: There is a high risk of Plasmodium vivax parasitaemia following treatment of falciparum malaria. Our study aimed to quantify this risk and the associated determinants using an individual patient data meta-analysis in order to identify populations in which a policy of universal radical cure, combining artemisinin-based combination therapy (ACT) with a hypnozoitocidal antimalarial drug, would be beneficial.

Methods and findings: A systematic review of Medline, Embase, Web of Science, and the Cochrane Database of Systematic Reviews identified efficacy studies of uncomplicated falciparum malaria treated with ACT that were undertaken in regions coendemic for P. vivax between 1 January 1960 and 5 January 2018. Data from eligible studies were pooled using standardised methodology. The risk of P. vivax parasitaemia at days 42 and 63 and associated risk factors were investigated by multivariable Cox regression analyses. Study quality was assessed using a tool developed by the Joanna Briggs Institute. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018097400). In total, 42 studies enrolling 15,341 patients were included in the analysis, including 30 randomised controlled trials and 12 cohort studies. Overall, 14,146 (92.2%) patients had P. falciparum monoinfection and 1,195 (7.8%) mixed infection with P. falciparum and P. vivax. The median age was 17.0 years (interquartile range [IQR] = 9.0-29.0 years; range = 0-80 years), with 1,584 (10.3%) patients younger than 5 years. 2,711 (17.7%) patients were treated with artemether-lumefantrine (AL, 13 studies), 651 (4.2%) with artesunate-amodiaquine (AA, 6 studies), 7,340 (47.8%) with artesunate-mefloquine (AM, 25 studies), and 4,639 (30.2%) with dihydroartemisinin-piperaquine (DP, 16 studies). 14,537 patients (94.8%) were enrolled from the Asia-Pacific region, 684 (4.5%) from the Americas, and 120 (0.8%) from Africa. At day 42, the cumulative risk of vivax parasitaemia following treatment of P. falciparum was 31.1% (95% CI 28.9-33.4) after AL, 14.1% (95% CI 10.8-18.3) after AA, 7.4% (95% CI 6.7-8.1) after AM, and 4.5% (95% CI 3.9-5.3) after DP. By day 63, the risks had risen to 39.9% (95% CI 36.6-43.3), 42.4% (95% CI 34.7-51.2), 22.8% (95% CI 21.2-24.4), and 12.8% (95% CI 11.4-14.5), respectively. In multivariable analyses, the highest rate of P. vivax parasitaemia over 42 days of follow-up was in patients residing in areas of short relapse periodicity (adjusted hazard ratio [AHR] = 6.2, 95% CI 2.0-19.5; p = 0.002); patients treated with AL (AHR = 6.2, 95% CI 4.6-8.5; p < 0.001), AA (AHR = 2.3, 95% CI 1.4-3.7; p = 0.001), or AM (AHR = 1.4, 95% CI 1.0-1.9; p = 0.028) compared with DP; and patients who did not clear their initial parasitaemia within 2 days (AHR = 1.8, 95% CI 1.4-2.3; p < 0.001). The analysis was limited by heterogeneity between study populations and lack of data from very low transmission settings. Study quality was high.

Conclusions: In this meta-analysis, we found a high risk of P. vivax parasitaemia after treatment of P. falciparum malaria that varied significantly between studies. These P. vivax

infections are likely attributable to relapses that could be prevented with radical cure including a hypnozoitocidal agent; however, the benefits of such a novel strategy will vary considerably between geographical areas.

Treatment of severe malaria

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Identifying prognostic factors of severe metabolic acidosis and uraemia in African children with severe falciparum malaria: a secondary analysis of a randomized trial

Grace Mzumara[1234], Stije Leopold[56], Kevin Marsh[57], Arjen Dondorp[56], Eric O Ohuma[#859], Mavuto Mukaka[#10856]

Abstract

Background: Severe metabolic acidosis and acute kidney injury are major causes of mortality in children with severe malaria but are often underdiagnosed in low resource settings.

Methods: A retrospective analysis of the 'Artesunate versus quinine in the treatment of severe falciparum malaria in African children' (AQUAMAT) trial was conducted to identify clinical features of severe metabolic acidosis and uraemia in 5425 children from nine African countries. Separate models were fitted for uraemia and severe metabolic acidosis. Separate univariable and multivariable logistic regression were performed to identify prognostic factors for severe metabolic acidosis and uraemia. Both analyses adjusted for the trial arm. A forward selection approach was used for model building of the logistic models and a threshold of 5% statistical significance was used for inclusion of variables into the final logistic model. Model performance was assessed through calibration, discrimination, and internal validation with bootstrapping.

Results: There were 2296 children identified with severe metabolic acidosis and 1110 with uraemia. Prognostic features of severe metabolic acidosis among them were deep breathing (OR: 3.94, CI 2.51-6.2), hypoglycaemia (OR: 5.16, CI 2.74-9.75), coma (OR: 1.72 CI 1.17-2.51), respiratory distress (OR: 1.46, CI 1.02-2.1) and prostration (OR: 1.88 CI 1.35-2.59). Features associated with uraemia were coma (3.18, CI 2.36-4.27), Prostration (OR: 1.78 CI 1.37-2.30), decompensated shock (OR: 1.89, CI 1.31-2.74), black water fever (CI 1.58. CI 1.09-2.27), jaundice (OR: 3.46 CI 2.21-5.43), severe anaemia (OR: 1.77, CI 1.36-2.29) and hypoglycaemia (OR: 2.77, CI 2.22-3.46) CONCLUSION: Clinical and laboratory parameters representing contributors and consequences of severe metabolic acidosis and uraemia were independently associated with these outcomes. The model can be useful for identifying patients at high risk of these complications where laboratory assessments are not routinely available.

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The effect of blood transfusion on outcomes among African children admitted to hospital with Plasmodium falciparum malaria: a prospective, multicentre observational study

Hans Ackerman[1], Aintzane Ayestaran[2], Christopher H O Olola[3], Muminatou Jallow[4], Tsiri Agbenyega[5], Kalifa Bojang[6], David J Roberts[7], Sanjeev Krishna[8], Peter G Kremsner[9], Charles R Newton[10], Terrie Taylor[11], Clarissa Valim[12], Climent Casals-Pascual[13]

Abstract

Background: Infection with Plasmodium falciparum leads to severe malaria and death in approximately 400 000 children each year in sub-Saharan Africa. Blood transfusion might benefit some patients with malaria but could potentially harm others. The aim of this study was to estimate the association between transfusion and death among children admitted to hospital with P falciparum malaria.

Methods: In this prospective, multicentre observational study, we analysed admissions to six tertiary care hospitals in The Gambia, Malawi, Gabon, Kenya, and Ghana that participated in the Severe Malaria in African Children network. Patients were enrolled if they were younger than 180 months and had a Giemsa-stained thick blood smear that was positive for P falciparum. Blood transfusion (whole blood at a target volume of 20 mL per kg) was administered at the discretion of the responsible physicians who were aware of local and international transfusion guidelines. The primary endpoint was death associated with transfusion, which was estimated using models adjusted for site and disease severity. We also aimed to identify factors associated with the decision to transfuse. The exploratory objective was to estimate optimal haemoglobin transfusion thresholds using generalised additive models.

Findings: Between Dec 19, 2000, and March 8, 2005, 26 106 patients were enrolled in the study, 25 893 of whom had their transfusion status recorded and were included in the primary analysis. 8513 (32·8%) patients received a blood transfusion. Patients were followed-up until discharge from hospital for a median of 2 days (IQR 1-4). 405 (4·8%) of 8513 patients who received a transfusion died compared with 689 (4·0%) of 17 380 patients who did not receive a transfusion. Transfusion was associated with decreased odds of death in site-adjusted analysis (odds ratio [OR] 0·82 [95% CI 0·71-0·94]) and after adjusting for the increased disease severity of patients who received a transfusion (0·50 [0·42-0·60]). Severe anaemia, elevated lactate concentration, respiratory distress, and parasite density were associated with greater odds of receiving a transfusion. Among all study participants, transfusion was associated with improved survival when the admission haemoglobin concentration was up to 77 g/L (95% CI 65-110). Among those with impaired consciousness (Blantyre Coma Score ≤4), transfusion was associated with improved survival at haemoglobin concentrations up to 105 g/L (95% CI 71-115). Among those with hyperlactataemia (blood lactate ≥5·0 mmol/L), transfusion was not significantly associated with harm at any haemoglobin concentration-ie, the OR of death comparing transfused versus not transfused was less than 1 at all haemoglobin concentrations (lower bound of the 95% CI for the haemoglobin concentration at which the OR of death equals 1: 90 g/L; no upper bound).

Interpretation: Our findings suggest that whole blood transfusion was associated with improved survival among children hospitalised with P falciparum malaria. Among those with impaired consciousness or hyperlactataemia, transfusion was associated with improved survival at haemoglobin concentrations above the currently recommended transfusion threshold. These findings highlight the need to do randomised controlled trials to test higher

transfusion thresholds among African children with severe malaria complicated by these factors.

*** Comment: not a randomized trial, but a well conducted controlled trial with a matched comparison group.

Malnutrition

(Papers in past years listed in this section refer to the management of protein-energy malnutrition. For other relevant studies of nutrition see also Nutrition, Vitamin A, Vitamin D, Zinc, Maternal health, Anaemia and iron deficiency)

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Effects of food supplementation on cognitive function, cerebral blood flow, and nutritional status in young children at risk of undernutrition: randomized controlled trial

Susan B Roberts[1], Maria A Franceschini[2], Rachel E Silver[3], Salima F Taylor[3], Augusto Braima de Sa[4], Raimundo Có[4], Aliu Sonco[4], Amy Krauss[5], Amy Taetzsch[3], Patrick Webb[3], Sai Krupa Das[3], C-Y Chen[6], Beatrice L Rogers[3], Edward Saltzman[3], Pei-Yi Lin[2], Nina Schlossman[3 7], William Pruzensky[4], Carlito Balé[4], Kenneth Kwan Ho Chui[8], Paul Muentener[9]

Abstract

Objective: To assess the effects of food supplementation on improving working memory and additional measures including cerebral blood flow in children at risk of undernutrition.

Design: Randomized controlled trial.

Setting: 10 villages in Guinea-Bissau.

Participants: 1059 children aged 15 months to 7 years; children younger than 4 were the primary population.

Interventions: Supervised isocaloric servings (≈1300 kJ, five mornings each week, 23 weeks) of a new food supplement (NEWSUP, high in plant polyphenols and omega 3 fatty acids, within a wide variety and high fortification of micronutrients, and a high protein content), or a fortified blended food (FBF) used in nutrition programs, or a control meal (traditional rice breakfast).

Main outcome measurements: The primary outcome was working memory, a core executive function predicting long term academic achievement. Additional outcomes were hemoglobin concentration, growth, body composition, and index of cerebral blood flow (CBF_i). In addition to an intention-to-treat analysis, a predefined per protocol analysis was conducted in children who consumed at least 75% of the supplement (820/925, 89%). The primary outcome was assessed by a multivariable Poisson model; other outcomes were assessed by multivariable linear mixed models.

Results: Among children younger than 4, randomization to NEWSUP increased working memory compared with the control meal (rate ratio 1.20, 95% confidence interval 1.02 to 1.41, P=0.03), with a larger effect in the per protocol population (1.25, 1.06 to 1.47, P=0.009). NEWSUP also increased hemoglobin concentration among children with anemia (adjusted

mean difference 0.65 g/dL, 95% confidence interval 0.23 to 1.07, P=0.003) compared with the control meal, decreased body mass index z score gain (-0.23, -0.43 to -0.02, P=0.03), and increased lean tissue accretion (2.98 cm^2, 0.04 to 5.92, P=0.046) with less fat (-5.82 cm^2, -11.28 to -0.36, P=0.04) compared with FBF. Additionally, NEWSUP increased CBF_i compared with the control meal and FBF in both age groups combined (1.14 $mm^2/s \times 10^{-8}$, 0.10 to 2.23, P=0.04 for both comparisons). Among children aged 4 and older, NEWSUP had no significant effect on working memory or anemia, but increased lean tissue compared with FBF (4.31 cm^2, 0.34 to 8.28, P=0.03).

Conclusions: Childhood undernutrition is associated with long term impairment in cognition. Contrary to current understanding, supplementary feeding for 23 weeks could improve executive function, brain health, and nutritional status in vulnerable young children living in low income countries. Further research is needed to optimize nutritional prescriptions for regenerative improvements in cognitive function, and to test effectiveness in other vulnerable groups.

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A Microbiota-Directed Food Intervention for Undernourished Children

Robert Y Chen[1], Ishita Mostafa[1], Matthew C Hibberd[1], Subhasish Das[1], Mustafa Mahfuz[1], Nurun N Naila[1], M Munirul Islam[1], Sayeeda Huq[1], M Ashraful Alam[1], Mahabub U Zaman[1], Arjun S Raman[1], Daniel Webber[1], Cyrus Zhou[1], Vinaik Sundaresan[1], Kazi Ahsan[1], Martin F Meier[1], Michael J Barratt[1], Tahmeed Ahmed[1], Jeffrey I Gordon[1]

Abstract

Background: More than 30 million children worldwide have moderate acute malnutrition. Current treatments have limited effectiveness, and much remains unknown about the pathogenesis of this condition. Children with moderate acute malnutrition have perturbed development of their gut microbiota.

Methods: In this study, we provided a microbiota-directed complementary food prototype (MDCF-2) or a ready-to-use supplementary food (RUSF) to 123 slum-dwelling Bangladeshi children with moderate acute malnutrition between the ages of 12 months and 18 months. The supplementation was given twice daily for 3 months, followed by 1 month of monitoring. We obtained weight-for-length, weight-for-age, and length-for-age z scores and mid-upper-arm circumference values at baseline and every 2 weeks during the intervention period and at 4 months. We compared the rate of change of these related phenotypes between baseline and 3 months and between baseline and 4 months. We also measured levels of 4977 proteins in plasma and 209 bacterial taxa in fecal samples.

Results: A total of 118 children (59 in each study group) completed the intervention. The rates of change in the weight-for-length and weight-for-age z scores are consistent with a benefit of MDCF-2 on growth over the course of the study, including the 1-month follow-up. Receipt of MDCF-2 was linked to the magnitude of change in levels of 70 plasma proteins and of 21 associated bacterial taxa that were positively correlated with the weight-for-length z score (P<0.001 for comparisons of both protein and bacterial taxa). These proteins included mediators of bone growth and neurodevelopment.

Conclusions: These findings provide support for MDCF-2 as a dietary supplement for young children with moderate acute malnutrition and provide insight into mechanisms by which this targeted manipulation of microbiota components may be linked to growth.

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Diagnostic measures for severe acute malnutrition in Indian infants under 6 months of age: a secondary data analysis

Ranadip Chowdhury[1], Nitika[2], Tarun Shankar Choudhary[2], Sunita Taneja[2], Jose Martines[3], Nita Bhandari[2], Rajiv Bahl[4]

Abstract

Background: Weight for length z-score (WLZ) < - 3 is currently used to define severe acute malnutrition (SAM) among infants. However, this approach has important limitations for infants younger than 6 months of age as WLZ cannot be calculated using WHO growth standards if infant length is < 45 cm. Moreover, length for age z-score (LAZ) and weight for length z-score (WLZ) are least reliable measures, with high chances of variation, and less chances of detecting undernutrition in under 6 months infants. The objective of the current analysis was to compare WLZ with WAZ and LAZ in a cohort of Indian infants in predicting the deaths between 6 weeks and 6 months of age.

Methods: The data was from an individually randomized trial conducted in slums of Delhi, India in which infants' weight and length were measured at 6 weeks of age (at the time of the first immunization visit). Vital status of the infants was documented from 6 weeks to 6 months of age. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for WAZ < -3, WLZ < -3, and LAZ < -3 for deaths between 6 weeks and 6 months of age. The receiver operating characteristics curve was calculated for each of the above anthropometric indicators.

Results: For deaths occurring between 6 weeks to 6 months of age, the specificity ranged between 85.9-95.9% for all three anthropometric indicators. However, the sensitivity was considerably higher for WAZ; it was 64.6% for WAZ < -3, 39.1% for LAZ < -3, and 25.0% for WLZ < -3. WAZ < -3 had higher area under curve (0.75; 95% CI: 0.68, 0.82) and hence, better discriminated deaths between 6 weeks and 6 months of age than WLZ < -3. The adjusted relative risk (RR 10.6, 95% CI 5.9, 18.9) and the population attributable fraction (PAF 57.9, 95% CI 38.8, 71.0%) of mortality was highest for WAZ < -3.

Conclusions: We found WAZ < -3 at 6 weeks of age to be a better predictor of death in the 6 weeks to 6 months of life in comparison to WLZ < -3 and LAZ < -3 and propose that it should be considered to diagnose SAM in this age group.

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Predictors of recovery in children aged 6-59 months with uncomplicated severe acute malnutrition: a multicentre study

Sam Marconi David[1], Preethi N Ragasudha[1], Sunita Taneja[2], Sanjana Brahmawar Mohan[3], Sharad D Iyengar[4], Ruby Angeline Pricilla[1], Jose Martines[5], Harshpal Singh

Sachdev[3], Virendra Suhalka[4], Venkata Raghava Mohan[1], Sarmila Mazumder[2], Ranadip Chowdhury[2], Rajiv Bahl[6], Anuradha Bose[1]

Abstract

Objective: To identify predictors of recovery in children with uncomplicated severe acute malnutrition (SAM).

Design: This is a secondary data analysis from an individual randomised controlled trial, where children with uncomplicated SAM were randomised to three feeding regimens, namely ready-to-use therapeutic food (RUTF) sourced from Compact India, locally prepared RUTF or augmented home-prepared foods, under two age strata (6-17 months and 18-59 months) for 16 weeks or until recovery. Three sets of predictors that could influence recovery, namely child, family and nutritional predictors, were analysed.

Setting: Rural and urban slum areas of three states of India, namely Rajasthan, Delhi and Tamil Nadu.

Participants: In total, 906 children (age: 6-59 months) were analysed to estimate the adjusted hazard ratio (AHR) using the Cox proportional hazard ratio model to identify various predictors.

Results: Being a female child (AHR: 1·269 (1·016, 1·584)), better employment status of the child's father (AHR: 1·53 (1·197, 1·95)) and residence in a rental house (AHR: 1·485 (1·137, 1·94)) increased the chances of recovery. No hospitalisation (AHR: 1·778 (1·055, 2·997)), no fever, (AHR: 2·748 (2·161, 3·494)) and ≤ 2 episodes of diarrhoea (AHR: 1·579 (1·035, 2·412)) during the treatment phase; availability of community-based peer support to mothers for feeding (AHR: 1·61 (1·237, 2·097)) and a better weight-for-height Z-score (WHZ) at enrolment (AHR: 1·811 (1·297, 2·529)) predicted higher chances of recovery from SAM.

Conclusion: The probability of recovery increases in children with better WHZ and with the initiation of treatment for acute illnesses to avoid hospitalisation, availability of peer support and better employment status of the father.

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A simplified, combined protocol versus standard treatment for acute malnutrition in children 6-59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan

Jeanette Bailey[1 2], Charles Opondo[3], Natasha Lelijveld[4], Bethany Marron[1], Pamela Onyo[5], Eunice N Musyoki[6], Susan W Adongo[6], Mark Manary[7], André Briend[8 9], Marko Kerac[2 10]

Abstract

Background: Malnutrition underlies 3 million child deaths worldwide. Current treatments differentiate severe acute malnutrition (SAM) from moderate acute malnutrition (MAM) with different products and programs. This differentiation is complex and costly. The Combined Protocol for Acute Malnutrition Study (ComPAS) assessed the effectiveness of a simplified, unified SAM/MAM protocol for children aged 6-59 months. Eliminating the need for separate products and protocols could improve the impact of programs by treating children more easily and cost-effectively, reaching more children globally.

Methods and findings: A cluster-randomized non-inferiority trial compared a combined protocol against standard care in Kenya and South Sudan. Randomization was stratified by country. Combined protocol clinics treated children using 2 sachets of ready-to-use

therapeutic food (RUTF) per day for those with mid-upper arm circumference (MUAC) < 11.5 cm and/or edema, and 1 sachet of RUTF per day for those with MUAC 11.5 to <12.5 cm. Standard care clinics treated SAM with weight-based RUTF rations, and MAM with ready-to-use supplementary food (RUSF). The primary outcome was nutritional recovery. Secondary outcomes included cost-effectiveness, coverage, defaulting, death, length of stay, and average daily weight and MUAC gains. Main analyses were per-protocol, with intention-to-treat analyses also conducted. The non-inferiority margin was 10%. From 8 May 2017 to 31 March 2018, 2,071 children were enrolled in 12 combined protocol clinics (mean age 17.4 months, 41% male), and 2,039 in 12 standard care clinics (mean age 16.7 months, 41% male). In total, 1,286 (62.1%) and 1,202 (59.0%), respectively, completed treatment; 981 (76.3%) on the combined protocol and 884 (73.5%) on the standard protocol recovered, yielding a risk difference of 0.03 (95% CI -0.05 to 0.10, p = 0.52; per-protocol analysis, adjusted for country, age, and sex). The amount of ready-to-use food (RUTF or RUSF) required for a child with SAM to reach full recovery was less in the combined protocol (122 versus 193 sachets), and the combined protocol cost US$123 less per child recovered (US$918 versus US$1,041). There were 23 (1.8%) deaths in the combined protocol arm and 21 (1.8%) deaths in the standard protocol arm (adjusted risk difference 95% CI -0.01 to 0.01, p = 0.87). There was no evidence of a difference between the protocols for any of the other secondary outcomes. Study limitations included contextual factors leading to defaulting, a combined multi-country power estimate, and operational constraints.
Conclusions: Combined treatment for SAM and MAM is non-inferior to standard care. Further research should focus on operational implications, cost-effectiveness, and context (Asia versus Africa; emergency versus food-secure settings). This trial is complete and registered at ISRCTN (ISRCTN30393230).

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doi: 10.1186/s41043-020-00222-x.

Determinants of stunting among children under 2 years in urban informal settlements in Mumbai, India: evidence from a household census

Sushmita Das[1], Sheila Chanani[2], Neena Shah More[2], David Osrin[3], Shanti Pantvaidya[2], Anuja Jayaraman[2]

Abstract
Background: There is limited evidence on the determinants of childhood stunting across urban India or specifically in slum settlements. This study aims to assess the extent of stunting among children under 2 years of age and examine its determinants in informal settlements of Mumbai.
Methods: Data were collected in 2014-2015 in a post intervention census of a cluster randomized controlled trial to improve the health of women and children. Census covered 40 slum settlements of around 600 households each. A total of 3578 children were included in the study. Mixed effects logistic regression models were used to identify factors associated with stunting.
Results: The prevalence of stunting among children aged 0-23 months was 38%. In the adjusted model, higher maternal education (AOR 0.59; 95% CI 0.42, 0.82), birth interval of at least 2 years (AOR 0.71; 95% CI 0.58, 0.87) and intended conception of the child (AOR 0.80; 95% CI 0.64, 0.99) were associated with lower odds of stunting. Maternal exposure to

physical violence (AOR 1.83; 95% CI 1.21, 2.77) was associated with higher odds of being stunted. A child aged 18-23 months had 5.04 times greater odds (95% CI 3.91, 6.5) of being stunted than a child less than 6 months of age. Male child had higher odds of being stunted (AOR 1.33; 95% CI 1.14, 1.54).
Conclusions: Our findings support a multidimensional aetiology for stunting. The results of the study emphasize the importance of women's status and decision-making power in urban India, along with access to and uptake of family planning and services to provide support for survivors of domestic violence. Ultimately, a multilateral effort is needed to ensure the success of nutrition-specific interventions by focusing on the underlying health and social status of women living in urban slums.

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doi: 10.1093/aje/kwaa139.
Incidence Correction Factors for Moderate and Severe Acute Child Malnutrition From 2 Longitudinal Cohorts in Mali and Burkina Faso
Francisco M Barba, Lieven Huybregts, Jef L Leroy
Abstract
Child acute malnutrition (AM) is an important cause of child mortality. Accurately estimating its burden requires cumulative incidence data from longitudinal studies, which are rarely available in low-income settings. In the absence of such data, the AM burden is approximated using prevalence estimates from cross-sectional surveys and the incidence correction factor K, obtained from the few available cohorts that measured AM. We estimated K factors for severe acute malnutrition (SAM) and moderate acute malnutrition (MAM) from AM incidence and prevalence using representative cross-sectional baseline and longitudinal data from 2 cluster-randomized controlled trials (Innovative Approaches for the Prevention of Childhood Malnutrition-PROMIS) conducted between 2014 and 2017 in Burkina Faso and Mali. We compared K estimates using complete (weight-for-length z score, mid-upper arm circumference (MUAC), and edema) and partial (MUAC, edema) definitions of SAM and MAM. K estimates for SAM were 9.4 and 5.7 in Burkina Faso and in Mali, respectively; K estimates for MAM were 4.7 in Burkina Faso and 5.1 in Mali. The MUAC and edema-based definition of AM did not lead to different K estimates. Our results suggest that K can be reliably estimated when only MUAC and edema-based data are available. Additional studies, however, are required to confirm this finding in different settings.

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Impact of food supplements on early child development in children with moderate acute malnutrition: A randomised 2 x 2 x 3 factorial trial in Burkina Faso
Mette F Olsen[1], Ann-Sophie Iuel-Brockdorff[1], Charles W Yaméogo[1 2], Bernardette Cichon[1], Christian Fabiansen[1], Suzanne Filteau[3], Kevin Phelan[4], Albertine Ouédraogo[4], Kim F Michaelsen[1], Melissa Gladstone[5], Per Ashorn[6], André Briend[1 6], Christian Ritz[1], Henrik Friis[1], Vibeke B Christensen[7 8]
Abstract

Background: Lipid-based nutrient supplements (LNS) and corn-soy blends (CSBs) with varying soy and milk content are used in treatment of moderate acute malnutrition (MAM). We assessed the impact of these supplements on child development.
Methods and findings: We conducted a randomised 2 × 2 × 3 factorial trial to assess the effectiveness of 12 weeks' supplementation with LNS or CSB, with either soy isolate or dehulled soy, and either 0%, 20%, or 50% of protein from milk, on child development among 6-23-month-old children with MAM. Recruitment took place at 5 health centres in Province du Passoré, Burkina Faso between September 2013 and August 2014. The study was fully blinded with respect to soy quality and milk content, while study participants were not blinded with respect to matrix. This analysis presents secondary trial outcomes: Gross motor, fine motor, and language development were assessed using the Malawi Development Assessment Tool (MDAT). Of 1,609 children enrolled, 54.7% were girls, and median age was 11.3 months (interquartile range [IQR] 8.2-16.0). Twelve weeks follow-up was completed by 1,548 (96.2%), and 24 weeks follow-up was completed by 1,503 (93.4%); follow-up was similar between randomised groups. During the study, 4 children died, and 102 children developed severe acute malnutrition (SAM). There was no difference in adverse events between randomised groups. At 12 weeks, the mean MDAT z-scores in the whole cohort had increased by 0.33 (95% CI: 0.28, 0.37), p < 0.001 for gross motor; 0.26 (0.20, 0.31), p < 0.001 for fine motor; and 0.14 (0.09, 0.20), p < 0.001 for language development. Children had larger improvement in language z-scores if receiving supplements with milk (20%: 0.09 [-0.01, 0.19], p = 0.08 and 50%: 0.11 [0.01, 0.21], p = 0.02), although the difference only reached statistical significance for 50% milk. Post hoc analyses suggested that this effect was specific to boys (interaction p = 0.02). The fine motor z-scores were also improved in children receiving milk, but only when 20% milk was added to CSB (0.18 [0.03, 0.33], p = 0.02). Soy isolate over dehulled soy increased language z-scores by 0.07 (-0.01, 0.15), p = 0.10, although not statistically significant. Post hoc analyses suggested that LNS benefited gross motor development among boys more than did CSB (interaction p = 0.04). Differences between supplement groups did not persist at 24 weeks, but MDAT z-scores continued to increase post-supplementation. The lack of an unsupplemented control group limits us from determining the overall effects of nutritional supplementation for children with MAM.
Conclusions: In this study, we found that child development improved during and after supplementation for treatment of MAM. Milk protein was beneficial for language and fine motor development, while suggested benefits related to soy quality and supplement matrix merit further investigation. Supplement-specific effects were not found post-intervention, but z-scores continued to improve, suggesting a sustained overall effect of supplementation.

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Effect of a newly developed ready-to-use supplementary food on growth indicators in children with mild to moderate malnutrition

F Azimi[1], A Esmaillzadeh[2], E Alipoor[3], M Moslemi[4], M Yaseri[5], M J Hosseinzadeh-Attar[6]

Abstract
Objectives: Malnutrition is one of the leading causes of death among children younger than five years. In this study, we aimed to formulate a ready-to-use supplementary food (RUSF),

based on local food products, and investigate its efficacy on growth indicators in children with mild to moderate malnutrition.
Study design: This is a randomized controlled clinical trial.
Methods: This study was performed in six health centers in Shahr-e-Rey, Tehran, Iran, between April and October 2017. One hundred children, aged 24-59 months, with mild to moderate malnutrition (weight-for-height Z-score [WHZ] between -3 and -1) were randomly assigned to two groups to receive either 1-3 sachets of RUSF or normal diet for 8 weeks. All mothers and caregivers received nutrition education. Growth indicators including weight and height, WHZ, and body mass index (BMI), along with clinical outcomes, were assessed.
Results: Children who received RUSF had a significant increase in weight (1.44 ± 0.38 vs 0.7 ± 0.32 kg, respectively, P < 0.001), and BMI (1.2 ± 0.47 vs 0.35 ± 0.33 kg/m^2, respectively, P < 0.001) compared with the control group. There was a greater daily weight gain during the first 4 weeks (P < 0.001) and throughout the study (P = 0.013) in the RUSF group. Daily height gain was considerably higher in the RUSF group during the first 4 weeks (P = 0.027). Children in the RUSF group had more improvement in WHZ (1.18 ± 0.41 vs 0.41 ± 0.31, P < 0.001) after supplementation. Besides, 92% of the RUSF and 12% of the control group reached to WHZ > -1 at the end of the study (P < 0.001). There was lower prevalence of diarrhea (12% vs 28.6%, respectively, P = 0.01) and marginally lower fever (16% vs 36.7%, respectively, P = 0.05) in the intervention than in the control group.
Conclusions: A newly developed RUSF improved growth indicators and clinical outcomes in children with mild to moderate malnutrition.

Nutrients. 2021 Mar 24;13(4):1054.
doi: 10.3390/nu13041054.

Response to Malnutrition Treatment in Low Weight-for-Age Children: Secondary Analyses of Children 6-59 Months in the ComPAS Cluster Randomized Controlled Trial

Jeanette Bailey[1,2], Natasha Lelijveld[3], Tanya Khara[3], Carmel Dolan[3], Heather Stobaugh[4], Kate Sadler[3], Richard Lino Lako[5], André Briend[6,7], Charles Opondo[8], Marko Kerac[2,9], Mark Myatt[10]

Abstract
Weight-for-age z-score (WAZ) is not currently an admission criterion to therapeutic feeding programs, and children with low WAZ at high risk of mortality may not be admitted. We conducted a secondary analysis of RCT data to assess response to treatment according to WAZ and mid-upper arm circumference (MUAC) and type of feeding protocol given: a simplified, combined protocol for severe and moderate acute malnutrition (SAM and MAM) vs. standard care that treats SAM and MAM, separately. Children with a moderately low MUAC (11.5-12.5 cm) and a severely low WAZ (<-3) respond similarly to treatment in terms of both weight and MUAC gain on either 2092 kJ (500 kcal)/day of therapeutic or supplementary food. Children with a severely low MUAC (<11.5 cm), with/without a severely low WAZ (<-3), have similar recovery with the combined protocol or standard treatment, though WAZ gain may be slower in the combined protocol. A limitation is this analysis was not powered for these sub-groups specifically. Adding WAZ < -3 as an admission criterion for therapeutic feeding programs admitting children with MUAC and/or oedema may help programs target

high-risk children who can benefit from treatment. Future work should evaluate the optimal treatment protocol for children with a MUAC < 11.5 and/or WAZ < -3.0.

Maternal health

(see also Malaria)

Int J Gynaecol Obstet. 2020 Oct;151(1):109-116.
doi: 10.1002/ijgo.13262. Epub 2020 Jul 27.

An integrated approach to improve maternal and perinatal outcomes in rural Guatemala: A stepped-wedge cluster randomized trial

Edgar Kestler[1], Guillermo Ambrosio[1], Karla Hemming[2], James P Hughes[3], Jorge Matute[4], Mario Moreno[5], Solange Madriz[6], Dilys Walker[6]

Abstract

Objective: To evaluate the impact of an intervention package on maternal and newborn health indicators.

Methods: A randomized stepped-wedge non-blind trial was conducted across six subdistricts within two districts in Guatemala from January 2014 to January 2017. Data on outcomes were collected on all deliveries in all 33 health centers. The intervention package included distribution of promotional materials encouraging health center delivery; education for traditional birth attendants about the importance of health center delivery; and provider capacity building using simulation training. Main outcomes were number of health center deliveries, maternal morbidity, and perinatal morbidity and mortality.

Results: Overall, there were 24 412 deliveries. Health center deliveries per 1000 live births showed an overall increase, although after adjustment for secular trends and clustering, the relative risk for the treatment effect was not statistically significant (aRR, 1.04; 95% confidence interval [CI], 0.97-1.11, P=0.242). Although not statistically significant, maternal morbidity (aRR, 0.78; 95% CI, 0.60-1.02; P=0.068) and perinatal morbidity (aRR, 0.84; 95% CI, 0.68-1.05; P=0.133) showed a tendency toward a decrease.

Conclusion: The present study represents one of the few randomized evaluations of an integrated approach to improve birth outcomes in a low-income setting.

Antenatal care

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Impact of group prenatal care on key prenatal services and educational topics in Malawi and Tanzania

Kylea L Liese[1], Esnath Kapito[2], Ellen Chirwa[2], Li Liu[3], Xiaohan Mei[3], Kathleen F Norr[1], Crystal L Patil[1]

Abstract

Objective: To examine whether group prenatal care (PNC) increased key services and educational topics women reported receiving, compared with individual PNC in Malawi and Tanzania.
Methods: Data come from a previously published randomized trial (n=218) and were collected using self-report surveys. Late pregnancy surveys asked whether women received all seven services and all 13 topics during PNC. Controlling for sociodemographics, country, and PNC attendance, multivariate logistic regression used forward selection to produce a final model showing predictors of receipt of all key services and topics.
Results: In multivariate logistic regression, women in group PNC were 2.49 times more likely to receive all seven services than those in individual care (95% confidence interval [CI] 1.78-3.48) and 5.25 times more likely to have received all 13 topics (95% CI 2.62-10.52).
Conclusion: This study provides strong evidence that group PNC meets the clinical standard of care for providing basic clinical services and perinatal education for pregnant women in sub-Saharan Africa. The greater number of basic PNC services and educational topics may provide one explanatory mechanism for how group PNC achieves its impact on maternal and neonatal outcomes.

BMC Pediatr. 2020 Oct 6;20(1):466.
doi: 10.1186/s12887-020-02363-8.

Effects of guided counseling during pregnancy on birth weight of newborns in West Gojjam Zone, Ethiopia: a cluster-randomized controlled trial

Yeshalem Mulugeta Demilew[1], Getu Degu Alene[2], Tefera Belachew[3]

Abstract
Background: The high proportion of birth weight in Ethiopia is hypothesized to be due to inadequate maternal diet which is associated with poor nutrition education during pregnancy. There was no study that evaluated the effect of nutrition education on birth weight in the study area. This study aimed to assess the effects (overall, direct and indirect effects) of guided counseling on the birth weight of neonates.
Methods: A two-arm parallel cluster randomized controlled community trial was conducted from May 1, 2018, to April 30, 2019, in West Gojjam Zone, Northwest Ethiopia. At the baseline, 346 pregnant women in the 11 intervention clusters and 348 pregnant women in the 11 control clusters were recruited. However, birth weight was measured from 258 and 272 newborns in the intervention and control groups, respectively. In the intervention group, counseling was given monthly for four consecutive months in the participant's homes. Besides, leaflets with key counseling messages were distributed to each woman in the intervention arm. Pregnant women who attended routine nutrition education given by the health system were recruited as control. Dietary practice, nutritional status, and birth weight were the primary, secondary and tertiary outcomes of this intervention. Data were collected using a structured data collection tool. Birth weight was measured within 48 h after birth. Independent sample t-test, linear mixed-effects model, and path analysis were fitted to assess effects of the intervention.
Results: The intra-cluster correlation coefficient was 0.095. The average birth weight of newborns in the intervention group was 0.257 kg higher compared with their counterparts in the control arm ($\beta = 0.257$, $P < 0.001$). The direct effect of this intervention on birth weight

was 0.17 (β = 0.17, P<0.001) whereas the indirect effect of this intervention was 0.08 (β = 0.08, P<0.001).
Conclusion: Counseling using the health belief model and the theory of planned behavior has a positive effect on improving birth weight. The findings suggest the need for enhancing nutrition education of pregnant women through the application of theories to improve birth weight.

Cochrane Database Syst Rev. 2020 Dec 18;12(12):CD009599.
doi: 10.1002/14651858.CD009599.pub2.
Antenatal interventions for preventing stillbirth, fetal loss and perinatal death: an overview of Cochrane systematic reviews
Erika Ota[1], Katharina da Silva Lopes[2], Philippa Middleton[3], Vicki Flenady[4], Windy Mv Wariki[5], Md Obaidur Rahman[6], Ruoyan Tobe-Gai[7], Rintaro Mori[8]
Abstract
Background: Stillbirth is generally defined as a death prior to birth at or after 22 weeks' gestation. It remains a major public health concern globally. Antenatal interventions may reduce stillbirths and improve maternal and neonatal outcomes in settings with high rates of stillbirth. There are several key antenatal strategies that aim to prevent stillbirth including nutrition, and prevention and management of infections.
Objectives: To summarise the evidence from Cochrane systematic reviews on the effects of antenatal interventions for preventing stillbirth for low risk or unselected populations of women.
Methods: We collaborated with Cochrane Pregnancy and Childbirth's Information Specialist to identify all their published reviews that specified or reported stillbirth; and we searched the Cochrane Database of Systematic Reviews (search date: 29 Feburary 2020) to identify reviews published within other Cochrane groups. The primary outcome measure was stillbirth but in the absence of stillbirth data, we used perinatal mortality (both stillbirth and death in the first week of life), fetal loss or fetal death as outcomes. Two review authors independently evaluated reviews for inclusion, extracted data and assessed quality of evidence using AMSTAR (A Measurement Tool to Assess Reviews) and GRADE tools. We assigned interventions to categories with graphic icons to classify the effectiveness of interventions as: clear evidence of benefit or harm; clear evidence of no effect or equivalence; possible benefit or harm; or unknown benefit or harm or no effect or equivalence.
Main results: We identified 43 Cochrane Reviews that included interventions in pregnant women with the potential for preventing stillbirth; all of the included reviews reported our primary outcome 'stillbirth' or in the absence of stillbirth, 'perinatal death' or 'fetal loss/fetal death'. AMSTAR quality was high in 40 reviews with scores ranging from 8 to 11 and moderate in three reviews with a score of 7. Nutrition interventions Clear evidence of benefit: balanced energy/protein supplementation versus no supplementation suggests a probable reduction in stillbirth (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.39 to 0.94, 5 randomised controlled trials (RCTs), 3408 women; moderate-certainty evidence). Clear evidence of no effect or equivalence for stillbirth or perinatal death: vitamin A alone versus placebo or no treatment; and multiple micronutrients with iron and folic acid versus iron

with or without folic acid. Unknown benefit or harm or no effect or equivalence: for all other nutrition interventions examined the effects were uncertain. Prevention and management of infections Possible benefit for fetal loss or death: insecticide-treated anti-malarial nets versus no nets (RR 0.67, 95% CI 0.47 to 0.97, 4 RCTs; low-certainty). Unknown evidence of no effect or equivalence: drugs for preventing malaria (stillbirth RR 1.02, 95% CI 0.76 to 1.36, 5 RCTs, 7130 women, moderate certainty in women of all parity; perinatal death RR 1.24, 95% CI 0.94 to 1.63, 4 RCTs, 5216 women, moderate-certainty in women of all parity). Prevention, detection and management of other morbidities Clear evidence of benefit: the following interventions suggest a reduction: midwife-led models of care in settings where the midwife is the primary healthcare provider particularly for low-risk pregnant women (overall fetal loss/neonatal death reduction RR 0.84, 95% CI 0.71 to 0.99, 13 RCTs, 17,561 women; high-certainty), training versus not training traditional birth attendants in rural populations of low- and middle-income countries (stillbirth reduction odds ratio (OR) 0.69, 95% CI 0.57 to 0.83, 1 RCT, 18,699 women, moderate-certainty; perinatal death reduction OR 0.70, 95% CI 0.59 to 0.83, 1 RCT, 18,699 women, moderate-certainty). Clear evidence of harm: a reduced number of antenatal care visits probably results in an increase in perinatal death (RR 1.14 95% CI 1.00 to 1.31, 5 RCTs, 56,431 women; moderate-certainty evidence). Clear evidence of no effect or equivalence: there was evidence of no effect in the risk of stillbirth/fetal loss or perinatal death for the following interventions and comparisons: psychosocial interventions; and providing case notes to women. Possible benefit: community-based intervention packages (including community support groups/women's groups, community mobilisation and home visitation, or training traditional birth attendants who made home visits) may result in a reduction of stillbirth (RR 0.81, 95% CI 0.73 to 0.91, 15 RCTs, 201,181 women; low-certainty) and perinatal death (RR 0.78, 95% CI 0.70 to 0.86, 17 RCTs, 282,327 women; low-certainty). Unknown benefit or harm or no effect or equivalence: the effects were uncertain for other interventions examined. Screening and management of fetal growth and well-being Clear evidence of benefit: computerised antenatal cardiotocography for assessing infant's well-being in utero compared with traditional antenatal cardiotocography (perinatal mortality reduction RR 0.20, 95% CI 0.04 to 0.88, 2 RCTs, 469 women; moderate-certainty). Unknown benefit or harm or no effect or equivalence: the effects were uncertain for other interventions examined.

Authors' conclusions: While most interventions were unable to demonstrate a clear effect in reducing stillbirth or perinatal death, several interventions suggested a clear benefit, such as balanced energy/protein supplements, midwife-led models of care, training versus not training traditional birth attendants, and antenatal cardiotocography. Possible benefits were also observed for insecticide-treated anti-malarial nets and community-based intervention packages, whereas a reduced number of antenatal care visits were shown to be harmful. However, there was variation in the effectiveness of interventions across different settings, indicating the need to carefully understand the context in which these interventions were tested. Further high-quality RCTs are needed to evaluate the effects of antenatal preventive interventions and which approaches are most effective to reduce the risk of stillbirth. Stillbirth (or fetal death), perinatal and neonatal death need to be reported separately in future RCTs of antenatal interventions to allow assessment of different interventions on these rare but important outcomes and they need to clearly define the target populations of women where the intervention is most likely to be of benefit. As the high burden of stillbirths occurs in low- and middle-income countries, further high-quality trials need to be conducted in these settings as a priority.

BMJ Glob Health. 2020 Dec;5(12):e003370.
doi: 10.1136/bmjgh-2020-003370.

Improving maternal, newborn and child health outcomes through a community-based women's health education program: a cluster randomised controlled trial in western Kenya

Lauren Y Maldonado[1 2], Jeffrey Bone[3], Michael L Scanlon[2 4], Gertrude Anusu[2], Sheilah Chelagat[2], Anjellah Jumah[2], Justus E Ikemeri[2], Julia J Songok[# 2 5], Astrid Christoffersen-Deb[# 3 6], Laura J Ruhl[# 2 7]

Abstract

Introduction: Community-based women's health education groups may improve maternal, newborn and child health (MNCH); however, evidence from sub-Saharan Africa is lacking. Chamas for Change (Chamas) is a community health volunteer (CHV)-led, group-based health education programme for pregnant and postpartum women in western Kenya. We evaluated Chamas' effect on facility-based deliveries and other MNCH outcomes.

Methods: We conducted a cluster randomised controlled trial involving 74 community health units in Trans Nzoia County. We included pregnant women who presented to health facilities for their first antenatal care visits by 32 weeks gestation. We randomised clusters 1:1 without stratification or matching; we masked data collectors, investigators and analysts to allocation. Intervention clusters were invited to bimonthly, group-based, CHV-led health lessons (Chamas); control clusters had monthly, individual CHV home visits (standard of care). The primary outcome was facility-based delivery at 12-month follow-up. We conducted an intention-to-treat approach with multilevel logistic regression models using individual-level data.

Results: Between 27 November 2017 and 8 March 2018, we enrolled 1920 participants from 37 intervention and 37 control clusters. A total of 1550 (80.7%) participants completed the study with 822 (82.5%) and 728 (78.8%) in the intervention and control arms, respectively. Facility-based deliveries improved in the intervention arm (80.9% vs 73.0%; risk difference (RD) 7.4%, 95% CI 3.0 to 12.5, OR=1.58, 95% CI 0.97 to 2.55, p=0.057). Chamas participants also demonstrated higher rates of 48 hours postpartum visits (RD 15.3%, 95% CI 12.0 to 19.6), exclusive breastfeeding (RD 11.9%, 95% CI 7.2 to 16.9), contraceptive adoption (RD 7.2%, 95% CI 2.6 to 12.9) and infant immunisation completion (RD 15.6%, 95% CI 11.5 to 20.9).

Conclusion: Chamas participation was associated with significantly improved MNCH outcomes compared with the standard of care. This trial contributes robust data from sub-Saharan Africa to support community-based, women's health education groups for MNCH in resource-limited settings.Trial registration numberNCT03187873.

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doi: 10.1093/jn/nxab108. Online ahead of print.

Baseline Hemoglobin, Hepcidin, Ferritin, and Total Body Iron Stores are Equally Strong Diagnostic Predictors of a Hemoglobin Response to 12 Weeks of Daily Iron Supplementation in Cambodian Women

Lulu X Pei[1], Hou Kroeun[2], Suzanne M Vercauteren[3 4], Susan I Barr[5], Tim J Green[6], Arianne Y Albert[7], Crystal D Karakochuk[4 5]

Abstract

Background: The WHO recommends daily iron supplementation for all women in areas where the population-level anemia prevalence is ≥40%, despite the fact that hemoglobin (Hb) concentration is generally considered to be a poor prognostic indicator of iron status.

Objectives: In this secondary analysis, we investigated the predictive power of ten baseline hematological biomarkers towards a 12-week Hb response to iron supplementation.

Methods: Data were obtained from a randomized controlled trial of daily iron supplementation in 407 nonpregnant Cambodian women (18-45 years) who received 60 mg elemental iron as ferrous sulfate for 12 weeks. Ten baseline biomarkers were included: Hb, measured with both a hematology analyzer and a HemoCue; inflammation-adjusted ferritin; soluble transferrin receptor; reticulocyte Hb; hepcidin; mean corpuscular volume; inflammation-adjusted total body iron stores (TBIS); total iron binding capacity; and transferrin saturation. Receiver operating characteristic (ROC) curves from fitted logistic regression models were used to make discrimination comparisons and variable selection methods were used to construct a multibiomarker prognostic model.

Results: Only 25% (n = 95/383) of women who completed the trial experienced a 12-week Hb response ≥10 g/L. The strongest univariate predictors of a Hb response were Hb as measured with a hematology analyzer, inflammation-adjusted ferritin, hepcidin, and inflammation-adjusted TBIS (AUCROC = 0.81, 0.83, 0.82, and 0.82, respectively), and the optimal cutoffs to identify women who were likely to experience a Hb response were 117 g/L, 17.3 µg/L, 1.98 nmol/L, and 1.95 mg/kg, respectively. Hb as measured with a hematology analyzer, inflammation-adjusted ferritin, and hepcidin had the best combined predictive ability (AUCROC=0.86). Hb measured with the HemoCue had poor discrimination ability (AUCROC = 0.65).

Conclusions: Baseline Hb as measured with a hematology analyzer was as strong a predictor of Hb response to iron supplementation as inflammation-adjusted ferritin, hepcidin, and inflammation-adjusted TBIS. This is positive given that the WHO currently uses the population-level anemia prevalence to guide recommendations for untargeted iron supplementation.

Maternal malaria prevention

Lancet Glob Health. 2020 Dec;8(12):e1524-e1533.
doi: 10.1016/S2214-109X(20)30386-7.

Cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperaquine versus single screening and treatment for the control of malaria in pregnancy in Papua, Indonesia: a provider perspective analysis from a cluster-randomised trial

Lucy Paintain[1], Jenny Hill[2], Rukhsana Ahmed[3], Chandra Umbu Reku Landuwulang[4], Ansariadi Ansariadi[5], Jeanne Rini Poespoprodjo[6], Din Syafruddin[4], Carole Khairallah[2], Faustina Helena Burdam[7], Irene Bonsapia[8], Feiko O Ter Kuile[2], Jayne Webster[9]

Abstract

Background: Malaria infection during pregnancy is associated with serious adverse maternal and birth outcomes. A randomised controlled trial in Papua, Indonesia, comparing the efficacy of intermittent preventive treatment with dihydroartemisinin-piperaquine with the current strategy of single screening and treatment showed that intermittent preventive treatment is a promising alternative treatment for the reduction of malaria in pregnancy. We aimed to estimate the incremental cost-effectiveness of intermittent preventive treatment with dihydroartemisinin-piperaquine compared with single screening and treatment with dihydroartemisinin-piperaquine.
Methods: We did a provider perspective analysis. A decision tree model was analysed from a health provider perspective over a lifetime horizon. Model parameters were used in deterministic and probabilistic sensitivity analyses. Simulations were run in hypothetical cohorts of 1000 women who received intermittent preventive treatment or single screening and treatment. Disability-adjusted life-years (DALYs) for fetal loss or neonatal death, low birthweight, moderate or severe maternal anaemia, and clinical malaria were calculated from trial data and cost estimates in 2016 US dollars from observational studies, health facility costings and public procurement databases. The main outcome measure was the incremental cost per DALY averted.
Findings: Relative to single screening and treatment, intermittent preventive treatment resulted in an incremental cost of US$5657 (95% CI 1827 to 9448) and 107·4 incremental DALYs averted (-719·7 to 904·1) per 1000 women; the average incremental cost-effectiveness ratio was $53 per DALY averted.
Interpretation: Intermittent preventive treatment with dihydroartemisinin-piperaquine offers a cost-effective alternative to single screening and treatment for the prevention of the adverse effects of malaria infection in pregnancy in the context of the moderate malaria transmission setting of Papua. The higher cost of intermittent preventive treatment was driven by monthly administration, as compared with single-administration single screening and treatment. However, acceptability and feasibility considerations will also be needed to inform decision making.

Malar J. 2020 Aug 5;19(1):282.
doi: 10.1186/s12936-020-03356-9.

A cluster randomized trial of delivery of intermittent preventive treatment of malaria in pregnancy at the community level in Burkina Faso

Julie R Gutman[1], Daniel K Stephens[2], Justin Tiendrebeogo[3], Ousmane Badolo[3], Mathurin Dodo[3], Danielle Burke[4], John Williamson[5], Kristen Vibbert[4], Susan J Youll[6], Yacouba Savadogo[7], William R Brieger[5]

Abstract
Background: Malaria in pregnancy is responsible for 8-14% of low birth weight and 20% of stillbirths in sub-Saharan Africa. To prevent these adverse consequences, the World Health Organization recommends intermittent preventive treatment of pregnant women (IPTp) with sulfadoxine-pyrimethamine be administered at each ANC visit starting as early as possible in the second trimester. Global IPTp coverage in targeted countries remains unacceptably low. Community delivery of IPTp was explored as a means to improve coverage.
Methods: A cluster randomized, controlled trial was conducted in 12 health facilities in a 1:1 ratio to either an intervention group (IPTp delivered by CHWs) or a control group (standard

practice, with IPTp delivered at HFs) in three districts of Burkina Faso to assess the effect of IPTp administration by community health workers (CHWs) on the coverage of IPTp and antenatal care (ANC). The districts and facilities were purposively selected taking into account malaria epidemiology, IPTp coverage, and the presence of active CHWs. Pre- and post-intervention surveys were carried out in March 2017 and July-August 2018, respectively. A difference in differences (DiD) analysis was conducted to assess the change in coverage of IPTp and ANC over time, accounting for clustering at the health facility level.
Results: Altogether 374 and 360 women were included in the baseline and endline surveys, respectively. At baseline, women received a median of 2.1 doses; by endline, women received a median of 1.8 doses in the control group and 2.8 doses in the intervention group (p-value < 0.0001). There was a non-statistically significant increase in the proportion of women attending four ANC visits in the intervention compared to control group (DiD = 12.6%, p-value = 0.16). By the endline, administration of IPTp was higher in the intervention than control, with a DiD of 17.6% for IPTp3 (95% confidence interval (CI) - 16.3, 51.5; p-value 0.31) and 20.0% for IPTp4 (95% CI - 7.2, 47.3; p-value = 0.15).
Conclusions: Community delivery of IPTp could potentially lead to a greater number of IPTp doses delivered, with no apparent decrease in ANC coverage.

J Infect Dis. 2020 Aug 4;222(5):863-870.
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Relationships Between Measures of Malaria at Delivery and Adverse Birth Outcomes in a High-Transmission Area of Uganda

John Ategeka[1], Abel Kakuru[1], Richard Kajubi[1], Razack Wasswa[1], Harriet Ochokoru[1], Emmanuel Arinaitwe[1,2], Adoke Yeka[1], Prasanna Jagannathan[3], Moses R Kamya[4], Atis Muehlenbachs[5], R Matthew Chico[2], Grant Dorsey[6]

Abstract
Background: Clinical trials of interventions for preventing malaria in pregnancy often use measures of malaria at delivery as their primary outcome. Although the objective of these interventions is to improve birth outcomes, data on associations between different measures of malaria at delivery and adverse birth outcomes are limited.
Methods: Data came from 637 Ugandan women enrolled in a randomized controlled trial of intermittent preventive treatment of malaria in pregnancy. Malaria at delivery was detected using peripheral and placental blood microscopy, placental blood loop-mediated isothermal amplification (LAMP), and placental histopathology. Multivariate analyses were used to estimate associations between measures of malaria at delivery and risks of low birth weight (LBW), small for gestational age (SGA), and preterm birth (PTB).
Results: Detection of malaria parasites by microscopy or LAMP was not associated with adverse birth outcomes. Presence of malaria pigment detected by histopathology in ≥30% of high-powered fields was strongly associated with LBW (adjusted risk ratio [aRR] = 3.42, P = .02) and SGA (aRR = 4.24, P < .001) but not PTB (aRR = 0.88, P = .87).
Conclusions: A semiquantitative classification system based on histopathologically detected malaria pigment provided the best surrogate measure of adverse birth outcomes in a high-transmission setting and should be considered for use in malaria in pregnancy intervention studies.

Lancet Glob Health. 2020 Jul;8(7):e942-e953.
doi: 10.1016/S2214-109X(20)30119-4.

Overall, anti-malarial, and non-malarial effect of intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine on birthweight: a mediation analysis

Michelle E Roh[1], Feiko O Ter Kuile[2], Francois Rerolle[3], M Maria Glymour[4], Stephen Shiboski[4], Roly Gosling[3], Julie Gutman[5], Abel Kakuru[6], Meghna Desai[5], Richard Kajubi[6], Anne L'Ianziva[7], Moses R Kamya[8], Grant Dorsey[9], R Matthew Chico[10]

Abstract

Background: Trials of intermittent preventive treatment (IPTp) of malaria in pregnant women that compared dihydroartemisinin-piperaquine with the standard of care, sulfadoxine-pyrimethamine, showed dihydroartemisinin-piperaquine was superior at preventing malaria infection, but not at improving birthweight. We aimed to assess whether sulfadoxine-pyrimethamine shows greater non-malarial benefits for birth outcomes than does dihydroartemisinin-piperaquine, and whether dihydroartemisinin-piperaquine shows greater antimalarial benefits for birth outcomes than does sulfadoxine-pyrimethamine.

Methods: We defined treatment as random assignment to sulfadoxine-pyrimethamine or dihydroartemisinin-piperaquine before pooling individual participant-level data from 1617 HIV-uninfected pregnant women in Kenya (one trial; n=806) and Uganda (two trials; n=811). We quantified the relative effect of treatment on birthweight (primary outcome) attributed to preventing placental malaria infection (mediator). We estimated antimalarial (indirect) and non-malarial (direct) effects of IPTp on birth outcomes using causal mediation analyses, accounting for confounders. We used two-stage individual participant data meta-analyses to calculate pooled-effect sizes.

Findings: Overall, birthweight was higher among neonates of women randomly assigned to sulfadoxine-pyrimethamine compared with women assigned to dihydroartemisinin-piperaquine (mean difference 69 g, 95% CI 26 to 112), despite placental malaria infection being lower in the dihydroartemisinin-piperaquine group (relative risk [RR] 0·64, 95% CI 0·39 to 1·04). Mediation analyses showed sulfadoxine-pyrimethamine conferred a greater non-malarial effect than did dihydroartemisinin-piperaquine (mean difference 87 g, 95% CI 43 to 131), whereas dihydroartemisinin-piperaquine conferred a slightly larger antimalarial effect than did sulfadoxine-pyrimethamine (8 g, -9 to 26), although more frequent dosing increased the antimalarial effect (31 g, 3 to 60).

Interpretation: IPTp with sulfadoxine-pyrimethamine appears to have potent non-malarial effects on birthweight. Further research is needed to evaluate monthly dihydroartemisinin-piperaquine with sulfadoxine-pyrimethamine (or another compound with non-malarial effects) to achieve greater protection against malarial and non-malarial causes of low birthweight.

Obstetric care and delivery

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doi: 10.1097/EDE.0000000000001224.

Antenatal Uterotonics as a Risk Factor for Intrapartum Stillbirth and First-day Death in Haryana, India: A Nested Case-control Study

Sanjana Brahmawar Mohan[1], Halvor Sommerfelt[2,3], J Frederik Frøen[2,3], Sunita Taneja[1], Tivendra Kumar[1], Kiran Bhatia[1], Lize van der Merwe[2], Rajiv Bahl[4], Jose C Martines[2], Sarmila Mazumder[1], Nita Bhandari[1]

Abstract

Background: Use of uterotonics like oxytocin to induce or augment labor has been shown to reduce placental perfusion and oxygen supply to the fetus, and studies indicate that it may increase the risk of stillbirth and neonatal asphyxia. Antenatal use of uterotonics, even without the required fetal monitoring and prompt access to cesarean section, is widespread, yet no study has adequately estimated the risk of intrapartum stillbirth and early neonatal deaths ascribed to such use. We conducted a case-control study to estimate this risk.

Methods: We conducted a population-based case-control study nested in a cluster-randomized trial. From 2008 to 2010, we followed pregnant women in rural Haryana, India, monthly until delivery. We visited all live-born infants on day 29 to ascertain whether they were alive. We conducted verbal autopsies for stillbirths and neonatal deaths. Cases (n = 2,076) were the intrapartum stillbirths and day-1 deaths (early deaths), and controls (n = 532) were live-born babies who died between day 8 and 28 (late deaths).

Results: Antenatal administration of uterotonics preceded 74% of early and 62% of late deaths, translating to an adjusted odds ratio (95% confidence interval [CI]) for early deaths of 1.7 (95% CI = 1.4, 2.1), and a population attributable risk of 31% (95% CI = 22%, 38%).

Conclusions: Antenatal administration of uterotonics was associated with a substantially increased risk of intrapartum stillbirth and day-1 death

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Preoperative vaginal cleansing with chlorhexidine solution in preventing post-cesarean section infections in a low resource setting: A randomized controlled trial

Christian O Ogah[1], Chidebe C Anikwe[1], Leonard O Ajah[1], Arinze C Ikeotuonye[1], Osaheni L Lawani[1], Bartholomew C Okorochukwu[2], Cyril C Ikeoha[1], Francis C Okoroafor[1]

Abstract

Introduction: Infection is one of the most common causes of maternal morbidities and mortality and has been reported to be responsible for about 15% of maternal deaths. Any woman is at risk of infection during childbirth, but women undergoing cesarean section are at higher risk. Improvement in surgical procedures with asepsis and the use of antibiotics have helped reduce postoperative infectious morbidities. However, ascending infection from the lower to the upper genital tract is a common but often neglected source of infection. Cleaning the vagina with chlorhexidine antiseptic solution before cesarean section can be a cheap and affordable source of infection control. This study is aimed at evaluating the

efficacy of preoperative vaginal cleansing using 1.0% chlorhexidine in the reduction of post-cesarean section infectious morbidities.
Material and methods: This prospective randomized control trial was conducted among 322 pregnant women who underwent an emergency cesarean section at Alex Ekwueme Federal University Teaching Hospital, Abakaliki (AE-FUTHA). The women were randomized into two groups. The interventional group received vaginal cleansing with three standard gauzes soaked in 30 mL 1.0% chlorhexidine gluconate solution preoperatively in addition to surgical skin cleaning with chlorhexidine-alcohol. The women in the control group only had surgical skin cleaning with chlorhexidine-alcohol. All the women received pre- and postoperative antibiotics. The primary outcomes were endometritis and wound infections.
Results: Infectious morbidity was significantly reduced from 36.8% in the control group to 12.0% in the intervention group (P = .001). Endometritis occurred significantly less frequently in the intervention group than the control group (respectively 6.6% compared with 27.6%: relative risk [RR] 0.29, 95% confidence interval [CI] 0.16-0.53; P < .05). Foul-smelling vaginal discharge was significantly more common in the control group than in the intervention group (11.8% vs 1.3%, respectively) but the CI was wide (RR 8.5, 95% CI 1.30-64.55; P < .001). Fever and wound infection were more common in the control group (5.9% vs 3.3% and 9.2% vs 5.3%) but the difference was not significant. The hospital stay was significantly shorter among the intervention group (5.54 ± 1.04 days compared with 6.01 ± 1.55 days, P < 0.05). The most common microbial isolate implicated in endocervical colonization was Staphylococcus aureus followed by Klebsiella species.
Conclusions: Vaginal cleansing with 1.0% chlorhexidine gluconate solution before emergency cesarean section appears to be effective in reducing rates of post-cesarean section infectious morbidity in the study area. We recommend its use among women undergoing cesarean section to help reduce the contribution of infections to a poor obstetrics outcome.

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Maternal oxygen exposure may not change umbilical cord venous partial pressure of oxygen: non-random, paired venous and arterial samples from a randomised controlled trial

Yunhai Chuai[1,2], Wen Jiang[2], Xiaobin Xu[3], Aiming Wang[2], Yuanqing Yao[4,5], Lei Chen[6,7]

Abstract
Background: Despite the widespread use of oxygen (O_2) in intrauterine resuscitation, the obstetric scientists' understanding of O_2 therapy is full of contradictions. We tested the hypothesis that higher maternal arterial partial pressure of oxygen (PO_2) is associated with higher umbilical cord venous PO_2 ($UvPO_2$).
Methods: This is a planned secondary analysis of a randomised controlled trial (RCT), 443 normal women were 1:1 randomly allocated to receive 2 L/min O_2 or room air from the onset of second stage to delivery. We reported that maternal 2 L/min O_2 exposure cannot affect the umbilical cord arterial pH or the fetal heart rate (FHR) pattern. In 217 non-random samples, we found 2 L/min O_2 exposure increased the maternal arterial PO_2 to the median 150 mmHg (hemoglobin would be saturated). The primary outcome for this analysis was $UvPO_2$ in these non-random samples.

Results: There were no significant differences between the O_2 group (N = 107) and the control group (N = 110) in the $UvPO_2$ (median 30.2, interquartile 25.4-35.2 versus median 28.3, interquartile 23.4-35.3, mmHg, P = 0.379). There were also no significant differences between room air and different percentiles of O_2 exposure duration (< 25th, ≧ 25th < 50th, ≧ 50th < 75th, ≧ 75th percentile) in the $UvPO_2$.
Conclusions: Maternal O_2 exposure at super-physiological levels (median arterial blood PO_2 150 mmHg) in normal labor may not change the $UvPO_2$.

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Does adherence to evidence-based practices during childbirth prevent perinatal mortality? A post-hoc analysis of 3,274 births in Uttar Pradesh, India

Katherine Ea Semrau[1 2 3], Kate A Miller[4], Stuart Lipsitz[4 3], Jennifer Fisher-Bowman[4 5], Ami Karlage[4], Bridget A Neville[4], Margaret Krasne[6], Jonathon Gass[4 7], Amanda Jurczak[4], Vinay Pratap Singh[8], Shambhavi Singh[8], Megan Marx Delaney[4], Lisa R Hirschhorn[9 10], Bhalachandra Kodkany[11], Vishwajeet Kumar[8], Atul A Gawande[4 12 13]

Abstract

Background: Evidence-based practices that reduce childbirth-related morbidity and mortality are core processes to quality of care. In the BetterBirth trial, a matched-pair, cluster-randomised controlled trial of a coaching-based implementation of the WHO Safe Childbirth Checklist (SCC) in Uttar Pradesh, India, we observed a significant increase in adherence to practices, but no reduction in perinatal mortality.
Methods: Within the BetterBirth trial, we observed birth attendants in a subset of study sites providing care to labouring women to assess the adherence to individual and groups of practices. We observed care from admission to the facility until 1 hour post partum. We followed observed women/newborns for 7-day perinatal health outcomes. Using this observational data, we conducted a post-hoc, exploratory analysis to understand the relationship of birth attendants' practice adherence to perinatal mortality.
Findings: Across 30 primary health facilities, we observed 3274 deliveries and obtained 7-day health outcomes. Adherence to individual practices, containing supply preparation and direct provider care, varied widely (0·51 to 99·78%). We recorded 166 perinatal deaths (50·71 per 1000 births), including 56 (17·1 per 1000) stillbirths. Each additional practice performed was significantly associated with reduced odds of perinatal (OR: 0·82, 95% CI: 0·72, 0·93) and early neonatal mortality (OR: 0·78, 95% CI: 0·71, 0·85). Each additional practice as part of direct provider care was associated strongly with reduced odds of perinatal (OR: 0·73, 95% CI: 0·62, 0·86) and early neonatal mortality (OR: 0·67, 95% CI: 0·56, 0·80). No individual practice or single supply preparation was associated with perinatal mortality.
Interpretation: Adherence to practices on the WHO SCC is associated with reduced mortality, indicating that adherence is a valid indicator of higher quality of care. However, the causal relationships between practices and outcomes are complex.

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Intravenous norepinephrine and mephentermine for maintenance of blood pressure during spinal anaesthesia for caesarean section: An interventional double-blinded randomised trial

Pratibha Jain Shah[1], Pratiksha Agrawal[1], Rajesh Kumar Beldar[1]

Abstract

Background and aims: Spinal anaesthesia induced hypotension (SAIH) and bradycardia may prove deleterious to both parturient and baby, hence vasopressors play a vital role in their management. Recent studies on norepinephrine as rescue vasopressor during subarachnoid block (SAB) enlighten its role for SAIH. This randomised double-blind trial was conducted to compare the effect of intermittent intravenous boluses of norepinephrine and frequently used mephentermine for management of SAIH in caesarean section (CS) to prove whether norepinephrine produces comparable effects or superior to mephentermine.

Methods: After approval from Institutional Ethics Committee and registration in Clinical Trials Registry India (CTRI/2019/06/019652), 256 parturients posted for elective CS under SAB were randomly allocated into Group-N and Group-M (n = 84) using chit system, who received boluses of intravenous norepinephrine 8µg and mephentermine 6mg for SAIH, respectively. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), Response%, Apgar score and maternal complications were analysed.

Results: The changes in SBP and DBP were comparable in both the groups. It was significantly low after SAB compared to baseline and significantly high compared to 1st hypotensive value in both the groups throughout the study period (<0.0001). HR was comparable for initial 10 min, thereafter it was significantly high in Group-M (<0.0001) till 40 min. Response% after the first bolus was significantly high in Group-N (59.30n ± 29.21 vs 39.78 ± 25.6; P = <0.0001).

Conclusion: Intravenous norepinephrine is better than mephentermine with respect to high response% and stable maternal HR although both are equally effective in maintaining blood pressure following SAIH during elective CS.

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Effect of hyoscine-N-butylbromide on labor duration among nullipara in a southwestern Nigerian teaching hospital: A randomized controlled trial

Adeniyi K Akiseku[1], Olusoji E Jagun[2], Adebayo A Akadri[3], John O Imaralu[3], Adetola O Olatunji[2], Adewale O Sule-Odu[2]

Abstract

Objective: To assess the effectiveness of hyoscine-N-butylbromide on the duration of the first stage of labor among nulliparous women.

Methods: A randomized double-blind placebo-controlled study among 126 nulliparous women admitted in the active phase of labor to a teaching hospital in Sagamu, Nigeria, from January to August 2018. Based on the inclusion criteria, women were recruited and randomized to the study or control group, and given intravenous hyoscine-N-butylbromide 20 mg (1 mL) or sterile water (1 mL), respectively, during the active phase. Labor progress and outcomes were compared between the groups.

Results: The mean ± SD duration of active phase of first stage of labor was significantly shorter in the hyoscine-N-butylbromide group (324.9 ± 134.6 min) than in the control group (392.7 ± 119.6 min) (P = 0.004). The rate of cervical dilatation was 1.4 ± 0.8 cm/h in the hyoscine-N-butylbromide group and 1.0 ± 0.5 cm/h in the control group (P = 0.004). There were no significant differences in fetal heart rate, maternal vital signs, or Apgar scores between the two groups.
Conclusion: Hyoscine-N-butylbromide was found to be effective in shortening the duration of the first stage of labor without adverse outcomes for mother or neonate.

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Effectiveness of upgraded maternity waiting homes and local leader training on improving institutional births: a cluster-randomized controlled trial in Jimma, Ethiopia

Jaameeta Kurji[1], Lakew Abebe Gebretsadik[2], Muluemebet Abera Wordofa[3], Sudhakar Morankar[2], Kunuz Haji Bedru[4], Gebeyehu Bulcha[4], Nicole Bergen[5], Getachew Kiros[2], Yisalemush Asefa[6], Shifera Asfaw[2], Abebe Mamo[2], Erko Endale[2], Kednapa Thavorn[7], Ronald Labonte[8], Monica Taljaard[9], Manisha A Kulkarni[8]

Abstract
Background: Maternity waiting homes (MWHs), residential spaces for pregnant women close to obstetric care facilities, are being used to tackle physical barriers to access. However, their effectiveness has not been rigorously assessed. The objective of this cluster randomized trial was to evaluate the effectiveness of functional MWHs combined with community mobilization by trained local leaders in improving institutional births in Jimma Zone, Ethiopia.
Methods: A pragmatic, parallel arm cluster-randomized trial was conducted in three districts. Twenty-four primary health care units (PHCUs) were randomly assigned to either (i) upgraded MWHs combined with local leader training on safe motherhood strategies, (ii) local leader training only, or (iii) usual care. Data were collected using repeat cross-sectional surveys at baseline and 21 months after intervention to assess the effect of intervention on the primary outcome, defined as institutional births, at the individual level. Women who had a pregnancy outcome (livebirth, stillbirth or abortion) 12 months prior to being surveyed were eligible for interview. Random effects logistic regression was used to evaluate the effect of the interventions.
Results: Data from 24 PHCUs and 7593 women were analysed using intention-to-treat. The proportion of institutional births was comparable at baseline between the three arms. At endline, institutional births were slightly higher in the MWH + training (54% [n = 671/1239]) and training only arms (65% [n = 821/1263]) compared to usual care (51% [n = 646/1271]). MWH use at baseline was 6.7% (n = 256/3784) and 5.8% at endline (n = 219/3809). Both intervention groups exhibited a non-statistically significant higher odds of institutional births compared to usual care (MWH$^+$ & leader training odds ratio [OR] = 1.09, 97.5% confidence interval [CI] 0.67 to 1.75; leader training OR = 1.37, 97.5% CI 0.85 to 2.22).
Conclusions: Both the combined MWH$^+$ & leader training and the leader training alone intervention led to a small but non-significant increase in institutional births when compared to usual care. Implementation challenges and short intervention duration may have hindered intervention effectiveness. Nevertheless, the observed increases suggest the

interventions have potential to improve women's use of maternal healthcare services. Optimal distances at which MWHs are most beneficial to women need to be investigated.

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Emergency Transportation Interventions for Reducing Adverse Pregnancy Outcomes in Low- and Middle-Income Countries: A Systematic Review

Halimatou Alaofe[1], Breanne Lott[1], Linda Kimaru[1], Babasola Okusanya[1], Abidemi Okechukwu[1], Joy Chebet[1], Martin Meremikwu[2], John Ehiri[1]

Abstract

Objective: To assess the effect of emergency transportation interventions on the outcome of labor and delivery in low- and middle-income countries (LMICs).

Methods: Eleven databases were searched through December 2019: Medline/PubMed, EMBASE, Web of Science, EBSCO (PsycINFO and CINAHL), SCIELO, LILACS, JSTOR, POPLINE, Google Scholar, the Cochrane Pregnancy and Childbirth Group's Specialized Register, and the Cochrane Central Register of Controlled Trials. Methodological quality of included studies was assessed using the ROBINS-I tool.

Results: Nine studies (three in Asia and six in Africa) were included: one cluster randomized controlled trial, three controlled before-and-after (CBA) studies, four uncontrolled before and after studies, and one case-control study. The means of emergency obstetric transportation evaluated by the studies included bicycle (n = 1) or motorcycle ambulances (n = 3), 4-wheel drive vehicles (n = 3), and formal motor-vehicle ambulances (n = 2). Transportation support was offered within multi-component interventions including financial incentives (n = 1), improved communication (n = 7), and community mobilization (n = 2). Two controlled before-and-after studies that implemented interventions including financial support, three-wheeled motorcycles, and use of mobile phones reported reduction of maternal mortality. One cluster-randomized study which involved community mobilization and strengthening of referral, and transportation, and one controlled before-and-after that implemented free-of-charge, 24-hour, 4 × 4 wheel ambulance and a mobile phone showed reductions in stillbirth, perinatal, and neonatal mortality. Six studies reported increases in facility delivery ranging from 12-50%, and one study showed a 19% reduction in home delivery. There was a significant increase of caesarian sections in two studies; use of motorcycle ambulances compared to car ambulance resulted in reduction in referral delay by 2 to 4.5 hours. Only three included studies had low risk of bias on all domains.

Conclusion: Integrating emergency obstetric transportation with complimentary maternal health interventions may reduce adverse pregnancy outcomes and increase access to skilled obstetric services for women in LMICs. The strength of evidence is limited by the paucity of high-quality studies.

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Randomized controlled trial comparing 400µg sublingual misoprostol versus placebo for prevention of primary postpartum hemorrhage

Rym Zgaya[1], Imen Ghadhab[1], Mohamed Amine Triki[2], Raja Briki[1]

Abstract

Introduction: obstetric hemorrhage is estimated to cause 25% of all maternal deaths and is the leading direct cause of maternal mortality worldwide. The World Health Organization recommended the use of uterotonics that should be offered for all women who will give birth but in some countries or in special situations oxytocin is not available. The goal of this study is to determine whether the 400µg dose of Misoprostol decreases the incidence of postpartum hemorrhage (PPH) of women who did not show signs of hemorrhage.

Methods: a prospective randomized double blind controlled trial was conducted between February 2012 and June 2012, among women in the active stage of labor attending the Obstetric Gynecology Department, University Hospital Farhat Hached of Sousse, Tunisia. Women with term singleton pregnancies greater than 32 weeks of amenorrhea with anticipated vaginal delivery were eligible for the study. Participants were randomly assigned to receive 400 µg sublingual Misoprostol or 2 ets of placebo immediately after cord clamping. The primary outcome measures were an estimation of blood loss including the subjective finding of vaginal hemorrhage > 500 ml, the decrease of hemoglobin and hematocrit, a change in hemodynamic parameters, and the need for additional dose of oxytocin. Secondary outcomes were occurrence of possible side effects such as: headache, nausea, vomiting, pyrexia, diarrhea and abdominal pain.

Results: a total of 211 patients were randomized: 111 in the Misoprostol group (Cytotec*) and 100 patients in the placebo group. The two groups were similar in terms of sociodemographic characteristics. Significant difference between the 400-µg of Misoprostol and placebo group were recorded in mean postpartum blood and PPH occurrence. The difference in pre- and postpartum hemoglobin loss (expressed in grams per 100 ml) was 1.21 ± 1.05 for the Misoprostol group and 1.51 ± 0.74 for the placebo group with significant difference (p = 0.02). No differences were observed in the occurrence of headache, dizziness, vomiting, diarrhea and metallic taste but the incidence of shivering was more than twice as great among women receiving Misoprostol than among those treated with placebo with a significant difference (p = 0.01). Similarly, women who received Misoprostol had a significantly higher mean temperature after delivery in comparison with those receiving placebo.

Conclusion: misoprostol, administered as 400 µg after delivery, appears to be effective for the prevention of post-partum hemorrhage, but its side effects appears to be significant.

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The WOMAN trial: clinical and contextual factors surrounding the deaths of 483 women following post-partum haemorrhage in developing countries

Roberto Picetti[1], Lori Miller[2], Haleema Shakur-Still[2], Tracey Pepple[2], Danielle Beaumont[2], Eni Balogun[2], Etienne Asonganyi[3], Rizwana Chaudhri[4], Mohamed El-Sheikh[5], Bellington Vwalika[6], Sabaratnam Arulkumaran[7], Ian Roberts[2], WOMAN trial collaborators

Abstract

Background: Post-partum haemorrhage (PPH) is a leading cause of maternal death worldwide. The WOMAN trial assessed the effects of tranexamic acid (TXA) on death and surgical morbidity in women with PPH. The trial recorded 483 maternal deaths. We report the circumstances of the women who died.
Methods: The WOMAN trial recruited 20,060 women with a clinical diagnosis of PPH after a vaginal birth or caesarean section. We randomly allocated women to receive TXA or placebo. When a woman died, we asked participating clinicians to report the cause of death and to provide a short narrative of the events surrounding the death. We collated and edited for clarity the narrative data.
Results: Case fatality rates were 3.0% in Africa and 1.7% in Asia. Nearly three quarters of deaths were within 3 h of delivery and 91% of these deaths were from bleeding. Women who delivered outside a participating hospital (12%) were three times more likely to die (OR = 3.12, 95%CI 2.55-3.81) than those who delivered in hospital. Blood was often unavailable due to shortages or because relatives could not afford to buy it. Clinicians highlighted late presentation, maternal anaemia and poor infrastructure as key contributory factors.
Conclusions: Although TXA use reduces bleeding deaths by almost one third, mortality rates similar to those in high income countries will not be achieved without tackling late presentation, maternal anaemia, availability of blood for transfusion and poor infrastructure.

Antenatal corticosterids

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Reducing neonatal mortality and respiratory distress syndrome associated with preterm birth: a scoping review on the impact of antenatal corticosteroids in low- and middle-income countries
Stanley Mwita[1], Mary Jande[2], Deogratias Katabalo[2], Benjamin Kamala[2], Deborah Dewey[2]
Abstract
Background: The most common cause of death among preterm infants in low- and middle-income countries is respiratory distress syndrome. The purpose of this review was to assess whether antenatal corticosteroids given to women at risk of preterm birth at ≤ 34 weeks of gestation reduce rates of neonatal mortality and respiratory distress syndrome in low- and middle-income countries.
Methods: Two reviewers independently searched four databases including MEDLINE (through PubMed), CINAHL, Embase, and Cochrane Libraries. We did not apply any language or date restrictions. All publications up to April 2020 were included in this search.
Results: The search yielded 71 articles, 10 of which were included in this review (3 randomized controlled trials, 7 observational studies, 36,773 neonates). The majority of studies reported associations between exposure to antenatal corticosteroids and lower rates of neonatal mortality and respiratory distress syndrome. However, a few studies reported that antenatal corticosteroids were not associated with improved preterm birth outcomes.
Conclusions: Most of the studies in low- and middle-income countries showed that use of antenatal corticosteroids in hospitals with high levels of neonatal care was associated with lower rates of neonatal mortality and respiratory distress syndrome. However, the findings

are inconclusive because some studies in low-resource settings reported that antenatal corticosteroids had no benefit in reducing rates of neonatal mortality or respiratory distress syndrome. Further research on the impact of antenatal corticosteroids in resource-limited settings in low-income countries is a priority.

Keywords: Antenatal corticosteroids; Low- and middle-income countries; Neonatal mortality;

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Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries

WHO ACTION Trials Collaborators; Olufemi T Oladapo[1], Joshua P Vogel[1], Gilda Piaggio[1], My-Huong Nguyen[1], Fernando Althabe[1], A Metin Gülmezoglu[1], Rajiv Bahl[1], Suman P N Rao[1], Ayesha De Costa[1], Shuchita Gupta[1], Abdullah H Baqui[1], Rasheda Khanam[1], Mohammod Shahidullah[1], Saleha B Chowdhury[1], Salahuddin Ahmed[1], Nazma Begum[1], Arunangshu D Roy[1], M A Shahed[1], Iffat A Jaben[1], Farida Yasmin[1], M Mozibur Rahman[1], Anjuman Ara[1], Soofia Khatoon[1], Gulshan Ara[1], Shaheen Akter[1], Nasreen Akhter[1], Probhat R Dey[1], M Abdus Sabur[1], Mohammad T Azad[1], Shahana F Choudhury[1], M A Matin[1], Shivaprasad S Goudar[1], Sangappa M Dhaded[1], Mrityunjay C Metgud[1], Yeshita V Pujar[1], Manjunath S Somannavar[1], Sunil S Vernekar[1], Veena R Herekar[1], Shailaja R Bidri[1], Sangamesh S Mathapati[1], Preeti G Patil[1], Mallanagouda M Patil[1], Muttappa R Gudadinni[1], Hidaytullah R Bijapure[1], Ashalata A Mallapur[1], Geetanjali M Katageri[1], Sumangala B Chikkamath[1], Bhuvaneshwari C Yelamali[1], Ramesh R Pol[1], Sujata S Misra[1], Leena Das[1], Saumya Nanda[1], Rashmita B Nayak[1], Bipsa Singh[1], Zahida Qureshi[1], Fredrick Were[1], Alfred Osoti[1], George Gwako[1], Ahmed Laving[1], John Kinuthia[1], Hafsa Mohamed[1], Nawal Aliyan[1], Adelaide Barassa[1], Elizabeth Kibaru[1], Margaret Mbuga[1], Lydia Thuranira[1], Njoroge J Githua[1], Bernadine Lusweti[1], Adejumoke I Ayede[1], Adegoke G Falade[1], Olubukola A Adesina[1], Atinuke M Agunloye[1], Oluwatosin O Iyiola[1], Wilfred Sanni[1], Ifeyinwa K Ejinkeonye[1], Hadiza A Idris[1], Chinyere V Okoli[1], Theresa A Irinyenikan[1], Omolayo A Olubosede[1], Olaseinde Bello[1], Olufemi M Omololu[1], Olanike A Olutekunbi[1], Adesina L Akintan[1], Olorunfemi O Owa[1], Rosena O Oluwafemi[1], Ireti P Eniowo[1], Adetokunbo O Fabamwo[1], Elizabeth A Disu[1], Joy O Agbara[1], Ebunoluwa A Adejuyigbe[1], Oluwafemi Kuti[1], Henry C Anyabolu[1], Ibraheem O Awowole[1], Akintunde O Fehintola[1], Bankole P Kuti[1], Anthony D Isah[1], Eyinade K Olateju[1], Olusanya Abiodun[1], Olabisi F Dedeke[1], Francis B Akinkunmi[1], Lawal Oyeneyin[1], Omotayo Adesiyun[1], Hadijat O Raji[1], Adedapo B A Ande[1], Ikechukwu Okonkwo[1], Shabina Ariff[1], Sajid B Soofi[1], Lumaan Sheikh[1], Saima Zulfiqar[1], Sadia Omer[1], Raheel Sikandar[1], Salma Sheikh[1], Daniel Giordano[1], Hugo Gamerro[1], Guillermo Carroli[1], Jose Carvalho[1], James Neilson[1], Elizabeth Molyneux[1], Khalid Yunis[1], Kidza Mugerwa[1], Harish K Chellani[1]

Abstract

Background: The safety and efficacy of antenatal glucocorticoids in women in low-resource countries who are at risk for preterm birth are uncertain.

Methods: We conducted a multicountry, randomized trial involving pregnant women between 26 weeks 0 days and 33 weeks 6 days of gestation who were at risk for preterm birth. The participants were assigned to intramuscular dexamethasone or identical placebo. The primary outcomes were neonatal death alone, stillbirth or neonatal death, and possible maternal bacterial infection; neonatal death alone and stillbirth or neonatal death were

evaluated with superiority analyses, and possible maternal bacterial infection was evaluated with a noninferiority analysis with the use of a prespecified margin of 1.25 on the relative scale.
Results: A total of 2852 women (and their 3070 fetuses) from 29 secondary- and tertiary-level hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan underwent randomization. The trial was stopped for benefit at the second interim analysis. Neonatal death occurred in 278 of 1417 infants (19.6%) in the dexamethasone group and in 331 of 1406 infants (23.5%) in the placebo group (relative risk, 0.84; 95% confidence interval [CI], 0.72 to 0.97; P = 0.03). Stillbirth or neonatal death occurred in 393 of 1532 fetuses and infants (25.7%) and in 444 of 1519 fetuses and infants (29.2%), respectively (relative risk, 0.88; 95% CI, 0.78 to 0.99; P = 0.04); the incidence of possible maternal bacterial infection was 4.8% and 6.3%, respectively (relative risk, 0.76; 95% CI, 0.56 to 1.03). There was no significant between-group difference in the incidence of adverse events.
Conclusions: Among women in low-resource countries who were at risk for early preterm birth, the use of dexamethasone resulted in significantly lower risks of neonatal death alone and stillbirth or neonatal death than the use of placebo, without an increase in the incidence of possible maternal bacterial infection.

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Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth
Emma McGoldrick[1], Fiona Stewart[2], Roses Parker[3], Stuart R Dalziel[4 5]
Abstract
Background: Respiratory morbidity including respiratory distress syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal mortality and disability. Despite early evidence indicating a beneficial effect of antenatal corticosteroids on fetal lung maturation and widespread recommendations to use this treatment in women at risk of preterm delivery, some uncertainty remains about their effectiveness particularly with regard to their use in lower-resource settings, different gestational ages and high-risk obstetric groups such as women with hypertension or multiple pregnancies. This updated review (which supersedes an earlier review Crowley 1996) was first published in 2006 and subsequently updated in 2017.
Objectives: To assess the effects of administering a course of corticosteroids to women prior to anticipated preterm birth (before 37 weeks of pregnancy) on fetal and neonatal morbidity and mortality, maternal mortality and morbidity, and on the child in later life.
Search methods: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (3 September 2020), ClinicalTrials.gov, the databases that contribute to the WHO International Clinical Trials Registry Platform (ICTRP) (3 September 2020), and reference lists of the retrieved studies.
Selection criteria: We considered all randomised controlled comparisons of antenatal corticosteroid administration with placebo, or with no treatment, given to women with a singleton or multiple pregnancy, prior to anticipated preterm delivery (elective, or following rupture of membranes or spontaneous labour), regardless of other co-morbidity, for inclusion in this review.

Data collection and analysis: We used standard Cochrane Pregnancy and Childbirth methods for data collection and analysis. Two review authors independently assessed trials for inclusion, assessed risk of bias, evaluated trustworthiness based on predefined criteria developed by Cochrane Pregnancy and Childbirth, extracted data and checked them for accuracy, and assessed the certainty of the evidence using the GRADE approach. Primary outcomes included perinatal death, neonatal death, RDS, intraventricular haemorrhage (IVH), birthweight, developmental delay in childhood and maternal death.
Main results: We included 27 studies (11,272 randomised women and 11,925 neonates) from 20 countries. Ten trials (4422 randomised women) took place in lower- or middle-resource settings. We removed six trials from the analysis that were included in the previous version of the review; this review only includes trials that meet our pre-defined trustworthiness criteria. In 19 trials the women received a single course of steroids. In the remaining eight trials repeated courses may have been prescribed. Fifteen trials were judged to be at low risk of bias, two had a high risk of bias in two or more domains and we ten trials had a high risk of bias due to lack of blinding (placebo was not used in the control arm. Overall, the certainty of evidence was moderate to high, but it was downgraded for IVH due to indirectness; for developmental delay due to risk of bias and for maternal adverse outcomes (death, chorioamnionitis and endometritis) due to imprecision. Neonatal/child outcomes Antenatal corticosteroids reduce the risk of: - perinatal death (risk ratio (RR) 0.85, 95% confidence interval (CI) 0.77 to 0.93; 9833 infants; 14 studies; high-certainty evidence; 2.3% fewer, 95% CI 1.1% to 3.6% fewer), - neonatal death (RR 0.78, 95% CI 0.70 to 0.87; 10,609 infants; 22 studies; high-certainty evidence; 2.6% fewer, 95% CI 1.5% to 3.6% fewer), - respiratory distress syndrome (RR 0.71, 95% CI 0.65 to 0.78; 11,183 infants; studies = 26; high-certainty evidence; 4.3% fewer, 95% CI 3.2% to 5.2% fewer). Antenatal corticosteroids probably reduce the risk of IVH (RR 0.58, 95% CI 0.45 to 0.75; 8475 infants; 12 studies; moderate-certainty evidence; 1.4% fewer, 95% CI 0.8% to1.8% fewer), and probably have little to no effect on birthweight (mean difference (MD) -14.02 g, 95% CI -33.79 to 5.76; 9551 infants; 19 studies; high-certainty evidence). Antenatal corticosteroids probably lead to a reduction in developmental delay in childhood (RR 0.51, 95% CI 0.27 to 0.97; 600 children; 3 studies; moderate-certainty evidence; 3.8% fewer, 95% CI 0.2% to 5.7% fewer). Maternal outcomes Antenatal corticosteroids probably result in little to no difference in maternal death (RR 1.19, 95% CI 0.36 to 3.89; 6244 women; 6 studies; moderate-certainty evidence; 0.0% fewer, 95% CI 0.1% fewer to 0.5% more), chorioamnionitis (RR 0.86, 95% CI 0.69 to 1.08; 8374 women; 15 studies; moderate-certainty evidence; 0.5% fewer, 95% CI 1.1% fewer to 0.3% more), and endometritis (RR 1.14, 95% CI 0.82 to 1.58; 6764 women; 10 studies; moderate-certainty; 0.3% more, 95% CI 0.3% fewer to 1.1% more) The wide 95% CIs in all of these outcomes include possible benefit and possible harm.
Authors' conclusions: Evidence from this updated review supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. Treatment with antenatal corticosteroids reduces the risk of perinatal death, neonatal death and RDS and probably reduces the risk of IVH. This evidence is robust, regardless of resource setting (high, middle or low). Further research should focus on variations in the treatment regimen, effectiveness of the intervention in specific understudied subgroups such as multiple pregnancies and other high-risk obstetric groups, and the risks and benefits in the very early or very late preterm periods. Additionally, outcomes from existing trials with follow-up into childhood and adulthood are needed in order to investigate any longer-term effects of antenatal corticosteroids. We encourage

authors of previous studies to provide further information which may answer any remaining questions about the use of antenatal corticosteroids without the need for further randomised controlled trials. Individual patient data meta-analyses from published trials are likely to provide answers for most of the remaining clinical uncertainties.

Maternal nutrition and micronutrient supplementation

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Does maternal iodine supplementation during the lactation have a positive impact on neurodevelopment of children? Three-year follow up of a randomized controlled trial
Pantea Nazeri[1], Zhale Tahmasebinejad[2], Elizabeth N Pearce[3], Zinat Zarezadeh[1], Tahere Tajeddini[1], Parvin Mirmiran[4,5], Fereidoun Azizi[6]
Abstract
Purpose: The aim of this study was to examine, for the first time, the neurodevelopmental outcomes in children whose mothers received different doses of iodine supplements during lactation.
Methods: We conducted a follow-up study on children whose mothers participated in a randomized clinical trial to receive placebo, 150 µg/day or 300 µg/day of iodine until 12 months postpartum. Child neurocognitive development was assessed at 36 months of age using the Bayley Scales of Infant and Toddler Development Third Edition. Linear mixed-model analysis was preformed to assess iodine supplement dose effects on child cognitive, language, and motor functions.
Results: A total of 122 children provided neurodevelopmental data as follows: 300 µg/d iodine group: 45; 150 µg/d iodine group: 35; and placebo group: 42. Cognitive scores were higher in children whose mothers received 150 µg iodine/d compared to children whose mothers received placebo [102.8 (SD 13.2) vs. 99.2 (SD 10.5); β = 4.43, P = 0.032]. However, supplementation with 150 µg iodine/d had no effect on language or motor development. No significant differences were observed in cognitive, language, or motor functions between children whose mothers received 300 µg iodine/d and those whose mothers received 150 µg iodine/d or placebo.
Conclusion: Maternal iodine supplementation with 150 µg/d during lactation may have a beneficial effect on child cognitive development; however, we found no evidence of either improved or delayed neurodevelopmental outcomes in children whose mothers received iodine supplements at doses higher than recommended. Further randomized controlled trials with larger sample sizes are needed to confirm these results.

Front Endocrinol (Lausanne). 2020 Oct 6;11:572984.
doi: 10.3389/fendo.2020.572984. eCollection 2020.
Iodine Supplementation in Mildly Iodine-Deficient Pregnant Women Does Not Improve Maternal Thyroid Function or Child Development: A Secondary Analysis of a Randomized Controlled Trial

Nicole J E Verhagen [1], Sueppong Gowachirapant [2], Pattanee Winichagoon [2], Maria Andersson [3], Alida Melse-Boonstra [1], Michael B Zimmermann [4]

Abstract

Background: Iodine deficiency during pregnancy may be associated with lower offspring IQ, but there are few data on the safety and efficacy of maternal iodine supplementation on child development. In a previously reported multi-center randomized trial conducted in Thailand and India, we assessed the effect of iodine supplementation in mildly iodine-deficient pregnant women on offspring development. In this secondary analysis of that trial, we report data only from the Thai pregnant women in the study, who were more iodine deficient at entry. **Methods:** Pregnant women in Bangkok, Thailand, were randomized to receive daily 200 µg oral iodine or placebo until delivery. We assessed thyroid size and thyroid function during pregnancy and cognitive and motor development at ages 1, 2, and 5.7 years. The trial was registered at www.clinicaltrials.gov/NCT00791466. **Findings:** Women (*n* = 514) entered the trial between November 2008 and March 2011 at a mean ± SD gestational age of 11 ± 2.8 weeks; their median (IQR) UIC was 112 (75, 170) µg/L. Mean compliance with supplementation was 88%. We assessed 397 mothers in the 3rd trimester, 231 infants at age 2 y, and 157 children at mean age 5.7 y. During pregnancy, there was a slightly greater decrease in free and total thyroxine concentrations in the iodine group ($p < 0.05$). At age 2 years, the iodine group had borderline lower scores for combined fine and gross motor function ($p = 0.05$), but there were no other significant differences in development. At 5.7 years, there were no significant group differences in child development. **Conclusion:** Daily iodine supplementation in mildly iodine deficient pregnant women was associated with small negative effects on maternal thyroxine concentrations, but did not affect child development. The safety and efficacy of iodine supplementation in mildly-iodine deficient pregnant women needs to be evaluated further in large randomized controlled trials.

BMC Womens Health. 2020 Nov 16;20(1):255.doi: 10.1186/s12905-020-01126-y.

Effect of nutrition education on iodine deficiency disorders and iodized salt intake in south west Ethiopian women: a cluster randomized controlled trial

Agize Asfaw [1], Tefera Belachew [2], Taye Gari [3]

Abstract

Background: Although iodine nutrition status is improving globally, the progress is not uniform throughout the world due to several factors. Among these, poor knowledge, negative attitude and improper practice of iodized salt are the main risk factors for poor iodine nutrition in Ethiopia. This study was aimed to assess the effect of nutrition education intervention on knowledge, attitude and practice (KAP) of iodine deficiency and iodized salt utilization.

Methods: A cluster randomized controlled trial was carried out among 652 women of reproductive age group in southwest Ethiopia. A total of 24 clusters were selected and randomized in to an intervention and control villages. Women in the intervention village received iodine nutrition related education for 6 months; while those in the control village did not receive any education. Baseline and endline data were collected from both groups. Generalized Estimating Equations (GEE) was used to determine the effect of intervention.

Results: A total of 647 (99.2%) participants were successfully involved in the study. In the intervention group the median attendance was 10 out of 12 sessions. Women in the intervention group had shown statistically significant change in knowledge, attitude and practice scores as compared to control one. In multivariable GEE linear model, after adjusting for other background characteristics, the mean difference (95% CI) scores were 8.81 (8.46, 9.16) for knowledge, 3.35 (3.17, 3.54) for attitude and 2.90 (2.74, 3.05) for practice in the intervention arm.
Conclusions: Well designed and community-based iodine nutrition education is an effective strategy to improve the KAP of iodine deficiency disorders and iodized salt utilization.

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Multiple-micronutrient supplementation in pregnant adolescents in low- and middle-income countries: a systematic review and a meta-analysis of individual participant data

Emily C Keats[1], Nadia Akseer[1], Pravheen Thurairajah[1], Simon Cousens[1], Zulfiqar A Bhutta[1], Global Young Women's Nutrition Investigators' Group

Abstract
Context: Approximately 7.3 million births occur annually among adolescents in low- and middle-income countries. Pregnant adolescents constitute a nutritionally vulnerable group that could benefit from intervention to mitigate the mortality and adverse birth outcomes associated with adolescent pregnancy.
Objective: The aim of this systematic review and meta-analysis was to assess the following: (1) the effect of multiple-micronutrient (MMN) supplementation vs iron and folic acid (IFA) supplementation among adolescents on maternal morbidity, birth outcomes, and mortality outcomes, (2) the effects of MMN supplementation in adolescents compared with the effects in adult women, and (3) the effect modification, if any, of MMN supplementation by baseline and geographic characteristics of adolescents.
Data sources: MEDLINE and Cochrane databases were searched, along with the reference lists of relevant reviews.
Study selection: Multiple-micronutrient supplementation trials in pregnancy that were conducted in a low- or middle-income country and had included at least 100 adolescents (10-19 years of age) were eligible for inclusion. Two independent reviewers assessed study eligibility.
Data extraction: Thirteen randomized controlled trials conducted in Africa and Asia were identified from 1792 reviews and 1578 original trials. Individual-level data was shared by study collaborators and was checked for completeness and extreme values. One- and two-stage individual participant data meta-analyses were conducted using data from randomized controlled trials of MMN supplementation.
Results: A total of 15 283 adolescents and 44 499 adult women with singleton births were included in the individual participant data meta-analyses of MMN supplementation vs IFA supplementation. In adolescents, MMN supplementation reduced low birth weight (1-stage OR = 0.87, 95%CI 0.77-0.97; 2-stage OR = 0.81; 95%CI 0.74-0.88), preterm birth (1-stage OR = 0.88, 95%CI 0.80-0.98; 2-stage OR = 0.86, 95%CI 0.79-0.95), and small-for-gestational-age

births (1-stage OR = 0.90, 95%CI 0.81-1.00; 2-stage OR = 0.86, 95%CI 0.79-0.95) when compared with IFA supplementation. The effects of MMN supplementation did not differ between adolescents and older women, although a potentially greater reduction in small-for-gestational-age births was observed among adolescents. Effect modification by baseline characteristics and geographic region was inconclusive.
Conclusions: Multiple-micronutrient supplementation can improve birth outcomes among pregnant adolescents in low- and middle-income countries. Policy related to antenatal care in these settings should prioritize MMN supplementation over the currently recommended IFA supplementation for all pregnant women, especially adolescents.

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Effects of prenatal and postnatal maternal multiple micronutrient supplementation on child growth and morbidity in Tanzania: a double-blind, randomized-controlled trial

Dongqing Wang[1], Uma Chandra Mouli Natchu[2], Anne Marie Darling[1], Ramadhani A Noor[3], Ellen Hertzmark[1], Willy Urassa[4], Wafaie W Fawzi[1 5 6]

Abstract
Background: Maternal micronutrient status is critical for child growth and nutrition. It is unclear whether maternal multiple micronutrient supplementation (MMS) during pregnancy and lactation improves child growth and prevents child morbidity.
Methods: This study aimed to determine the effects of prenatal and postnatal maternal MMS on child growth and morbidity. In this double-blind, randomized-controlled trial, 8428 HIV-negative pregnant women were enrolled from Dar es Salaam, Tanzania, between 2001 and 2004. From pregnancy (12-27 weeks of gestation) through to 6 weeks postpartum, participants were randomized to receive daily oral MMS or placebo. All women received daily iron and folic acid during pregnancy. From 6 weeks postpartum through to 18 months postpartum, 3100 women were re-randomized to MMS or placebo. Child-growth measures, haemoglobin concentrations and infectious morbidities were assessed longitudinally from birth to ≤18 months.
Results: Prenatal MMS led to modest increases in weight-for-age z-scores (mean difference: 0.050; 95% confidence interval: 0.002, 0.099; p = 0.04) and length-for-age z-score (mean difference: 0.062; 95% confidence interval: 0.013, 0.111; p = 0.01) during the first 6 months of life but not thereafter. Prenatal or postnatal MMS did not have benefits for other child outcomes.
Conclusions: Whereas maternal MMS is a proven strategy to prevent adverse birth outcomes, other approaches may also need to be considered to curb the high burdens of child morbidity and growth faltering.

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Low-dose thiamine supplementation of lactating Cambodian mothers improves human milk thiamine concentrations: a randomized controlled trial

Jelisa Gallant[1], Kathleen Chan[1], Tim J Green[2,3], Frank T Wieringa[4], Shalem Leemaqz[2], Rem Ngik[5], Jeffrey R Measelle[6], Dare A Baldwin[6], Mam Borath[7], Prak Sophonneary[8], Lisa N Yelland[2,9], Daniela Hampel[10,11], Setareh Shahab-Ferdows[10,11], Lindsay H Allen[10,11], Kerry S Jones[12], Albert Koulman[12], Damon A Parkington[12], Sarah R Meadows[12], Hou Kroeun[5], Kyly C Whitfield[1]

Abstract

Background: Infantile beriberi-related mortality is still common in South and Southeast Asia. Interventions to increase maternal thiamine intakes, and thus human milk thiamine, are warranted; however, the required dose remains unknown.

Objectives: We sought to estimate the dose at which additional maternal intake of oral thiamine no longer meaningfully increased milk thiamine concentrations in infants at 24 wk postpartum, and to investigate the impact of 4 thiamine supplementation doses on milk and blood thiamine status biomarkers.

Methods: In this double-blind, 4-parallel arm randomized controlled dose-response trial, healthy mothers were recruited in Kampong Thom, Cambodia. At 2 wk postpartum, women were randomly assigned to consume 1 capsule, containing 0, 1.2 (estimated average requirement), 2.4, or 10 mg of thiamine daily from 2 through 24 weeks postpartum. Human milk total thiamine concentrations were measured using HPLC. An Emax curve was plotted, which was estimated using a nonlinear least squares model in an intention-to-treat analysis. Linear mixed-effects models were used to test for differences between treatment groups. Maternal and infant blood thiamine biomarkers were also assessed.

Results: In total, each of 335 women was randomly assigned to1 of the following thiamine-dose groups: placebo (n = 83), 1.2 mg (n = 86), 2.4 mg (n = 81), and 10 mg (n = 85). The estimated dose required to reach 90% of the maximum average total thiamine concentration in human milk (191 μg/L) is 2.35 (95% CI: 0.58, 7.01) mg/d. The mean ± SD milk thiamine concentrations were significantly higher in all intervention groups (183 ± 91, 190 ± 105, and 206 ± 89 μg/L for 1.2, 2.4, and 10 mg, respectively) compared with the placebo group (153 ± 85 μg/L; $P < 0.0001$) and did not significantly differ from each other.

Conclusions: A supplemental thiamine dose of 2.35 mg/d was required to achieve a milk total thiamine concentration of 191 μg/L. However, 1.2 mg/d for 22 wk was sufficient to increase milk thiamine concentrations to similar levels achieved by higher supplementation doses (2.4 and 10 mg/d), and comparable to those of healthy mothers in regions without beriberi.

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Thiamine supplementation holds neurocognitive benefits for breastfed infants during the first year of life

Jeffrey R Measelle[1], Dare A Baldwin[1], Jelisa Gallant[2], Kathleen Chan[2], Tim J Green[3], Frank T Wieringa[4], Mam Borath[5], Sophonneary Prak[6], Daniela Hampel[7,8], Setareh Shahab-Ferdows[7,8], Lindsay H Allen[7,8], Hou Kroeun[9], Kyly C Whitfield[2]

Abstract

Women reliant on mostly rice-based diets can have inadequate thiamine intake, placing breastfed infants at risk of thiamine deficiency and, in turn, physical and cognitive impairments. We investigated the impact of maternal thiamine supplementation doses on infants' cognitive, motor, and language development across the first year. In this double-blind, four-parallel-arm, randomized controlled trial, healthy mothers of exclusively breastfed newborn infants were recruited in Kampong Thom, Cambodia. At 2 weeks postnatal, women (n = 335) were randomized to one of four treatment groups to consume one capsule/day with varying amounts of thiamine for 22 weeks: 0, 1.2, 2.4, and 10 mg. At 2, 12, 24, and 52 weeks of age, infants were assessed with the Mullen Scales of Early Learning (MSEL) and the Caregiver Reported Early Development Instrument (CREDI). Multiple regression and mixed effects modeling suggest that by 6 months of age, the highest maternal thiamine dose (10 mg/day) held significant benefits for infants' language development, but generally not for motor or visual reception development. Despite having achieved standardized scores on the MSEL that approximated U.S. norms by 6 months, infants showed a significant drop relative to these norms in both language domains following trial completion, indicating that nutritional interventions beyond 6 months may be necessary.

J Nutr. 2020 Jul 1;150(7):1951-1957.
doi: 10.1093/jn/nxaa123.

Vitamin B-12 Supplementation during Pregnancy and Early Lactation Does Not Affect Neurophysiologic Outcomes in Children Aged 6 Years

Krishnamachari Srinivasan[1], Susan Thomas[1], Shilpa Anand[1], Mahesh Jayachandra[1], Tinku Thomas[2], Tor Arne Strand[3], Anura V Kurpad[4], Christopher P Duggan[5]

Abstract

Background: Deficiency of vitamin B-12 is common in pregnant Indian women. Assessment of neurophysiological measures using event-related potentials (ERPs) may yield additional information on the effects of maternal B-12 supplementation on child brain function.

Objectives: The objective of the study was to evaluate the effects of vitamin B-12 supplementation (50 μg daily orally) during pregnancy on the childhood ERP measures of positive waveform ~300 ms after stimulus (P300) and mismatch negativity.

Methods: This study was a follow-up of children born to pregnant women who received oral vitamin B-12 supplements (n = 62) compared with children of pregnant women who received placebo (n = 70) from a randomized controlled trial. The mean ± SD child age was 72 ± 1 mo. We used the Enobio system to assess the ERP measures P300 and mismatch negativity.

Results: There were no significant differences in the primary outcomes, amplitudes, and latencies of the P300 results and the mismatch negativity between children in the supplementation and placebo groups. We combined the intervention and placebo groups for secondary analyses. On multiple variable regression analysis after adjusting for treatment group, intrauterine growth restriction, and home environment, P300 amplitude in children was significantly higher in the lowest tertile of third-trimester maternal methylmalonic acid (MMA) concentrations (β = 3034.04; 95% CI: 923.24, 5144.83) compared with the highest MMA tertile (β = 1612.12; 95% CI: -258.86, 3483.10, P = 0.005).

Conclusions: While no significant effects of maternal vitamin B-12 supplementation on children's ERP measures were seen at 72 mo, elevated maternal MMA concentrations in the

third trimester were negatively associated with P300 amplitude in children. It may be worthwhile to study the impact of maternal and infant vitamin B-12 supplementation on childhood brain structure and function in longer and larger trials.

J Nutr. 2020 Dec 10;150(12):3094-3102.
doi: 10.1093/jn/nxaa267.

Iron Absorption from Iron-Biofortified Sweetpotato Is Higher Than Regular Sweetpotato in Malawian Women while Iron Absorption from Regular and Iron-Biofortified Potatoes Is High in Peruvian Women

Roelinda Jongstra[1], Martin N Mwangi[2], Gabriela Burgos[3], Christophe Zeder[1], Jan W Low[4], Glory Mzembe[2], Reyna Liria[5], Mary Penny[5], Maria I Andrade[6], Susan Fairweather-Tait[7], Thomas Zum Felde[3], Hugo Campos[3], Kamija S Phiri[2], Michael B Zimmermann[1], Rita Wegmüller[1,8]

Abstract

Background: Sweetpotato and potato are fast-maturing staple crops and widely consumed in low- and middle-income countries. Conventional breeding to biofortify these crops with iron could improve iron intakes. To our knowledge, iron absorption from sweetpotato and potato has not been assessed.

Objective: The aim was to assess iron absorption from regular and iron-biofortified orange-fleshed sweetpotato in Malawi and yellow-fleshed potato and iron-biofortified purple-fleshed potato in Peru.

Methods: We conducted 2 randomized, multiple-meal studies in generally healthy, iron-depleted women of reproductive age. Malawian women (n = 24) received 400 g regular or biofortified sweetpotato test meals and Peruvian women (n = 35) received 500 g regular or biofortified potato test meals. Women consumed the meals at breakfast for 2 wk and were then crossed over to the other variety. We labeled the test meals with 57Fe or 58Fe and measured cumulative erythrocyte incorporation of the labels 14 d after completion of each test-meal sequence to calculate iron absorption. Iron absorption was compared by paired-sample t tests.

Results: The regular and biofortified orange-fleshed sweetpotato test meals contained 0.55 and 0.97 mg Fe/100 g. Geometric mean (95% CI) fractional iron absorption (FIA) was 5.82% (3.79%, 8.95%) and 6.02% (4.51%, 8.05%), respectively (P = 0.81), resulting in 1.9-fold higher total iron absorption (TIA) from biofortified sweetpotato (P < 0.001). The regular and biofortified potato test meals contained 0.33 and 0.69 mg Fe/100 g. FIA was 28.4% (23.5%, 34.2%) from the regular yellow-fleshed and 13.3% (10.6%, 16.6%) from the biofortified purple-fleshed potato meals, respectively (P < 0.001), resulting in no significant difference in TIA (P = 0.88).

Conclusions: FIA from regular yellow-fleshed potato was remarkably high, at 28%. Iron absorbed from both potato test meals covered 33% of the daily absorbed iron requirement for women of reproductive age, while the biofortified orange-fleshed sweetpotato test meal covered 18% of this requirement. High polyphenol concentrations were likely the major inhibitors of iron absorption.

Lancet Glob Health. 2021 Feb;9(2):e189-e198.
doi: 10.1016/S2214-109X(20)30448-4. Epub 2020 Nov 24.

Efficacy and safety of intravenous ferric carboxymaltose compared with oral iron for the treatment of iron deficiency anaemia in women after childbirth in Tanzania: a parallel-group, open-label, randomised controlled phase 3 trial

Fiona Vanobberghen[1], Omar Lweno[2], Andrea Kuemmerle[3], Kwaba Dennis Mwebi[2], Peter Asilia[4], Amina Issa[2], Beatus Simon[2], Sarah Mswata[2], Sandro Schmidlin[3], Tracy R Glass[3], Salim Abdulla[2], Claudia Daubenberger[3], Marcel Tanner[3], Sandrine Meyer-Monard[5]

Abstract

Background: Iron deficiency anaemia is of major concern in low-income settings, especially for women of childbearing age. Oral iron substitution efficacy is limited by poor compliance and iron depletion severity. We aimed to assess the efficacy and safety of intravenous ferric carboxymaltose versus oral iron substitution following childbirth in women with iron deficiency anaemia in Tanzania.

Methods: This parallel-group, open-label, randomised controlled phase 3 trial was done at Bagamoyo District Hospital and Mwananyamala Hospital, Tanzania. Eligible participants were close to delivery and had iron deficiency anaemia defined as a haemoglobin concentration of less than 110 g/L and a ferritin concentration of less than 50 µg/L measured within 14 days before childbirth. Participants were randomly assigned 1:1 to receive intravenous ferric carboxymaltose or oral iron, stratified by haemoglobin concentration and site. Intravenous ferric carboxymaltose was administered at a dose determined by the haemoglobin concentration and bodyweight (bodyweight 35 kg to <70 kg and haemoglobin ≥100 g/L: 1000 mg in one dose; bodyweight 35 kg to <70 kg and haemoglobin <100 g/L, or bodyweight ≥70 kg and haemoglobin ≥100 g/L: 1500 mg in two doses at least 7 days apart; bodyweight ≥70 kg and haemoglobin <100 g/L: 2000 mg in two doses at least 7 days apart). Oral iron treatment consisted of three dried ferrous sulphate tablets of 200 mg containing 60 mg of elementary iron and 5 mg of folic acid every morning. Oral treatment was to be taken for 3 months after haemoglobin normalisation. The primary outcome was haemoglobin normalisation (>115 g/L) at 6 weeks. Follow-up visits were at 6 weeks, and 3, 6, and 12 months. Analyses were done in the modified intention-to-treat population of participants who had a 6-week haemoglobin concentration result, using logistic and linear regression models for binary and continuous outcomes, adjusted for baseline haemoglobin concentration and site. This trial is registered with ClinicalTrials.gov, NCT02541708.

Findings: Between Oct 8, 2015, and March 14, 2017, 533 individuals were screened and 230 were enrolled and randomly assigned to a study group (114 to intravenous iron, 116 to oral iron). At 6 weeks, 94 (82%) participants in the intravenous iron group and 92 (79%) in the oral iron group were assessed for the primary outcome. 75 (80%) participants in the intravenous iron group and 47 (51%) in the oral iron group had normalised haemoglobin (odds ratio 4·65, 95% CI 2·33-9·27). There were two mild to moderate infusion-related adverse events; and five serious adverse events (three in the intravenous iron group, two in the oral iron group), unrelated to the study medication.

Interpretation: Intravenous iron substitution with ferric carboxymaltose was safe and yielded a better haemoglobin response than oral iron. To our knowledge, this is the first study to provide evidence of the benefits and safety of intravenous iron substitution in a low-income setting.

Nutrients. 2020 Oct 3;12(10):3041.
doi: 10.3390/nu12103041.

Effect of Maternal Docosahexaenoic Acid (DHA) Supplementation on Offspring Neurodevelopment at 12 Months in India: A Randomized Controlled Trial

Shweta Khandelwal[1,2], Dimple Kondal[1,2], Monica Chaudhry[1], Kamal Patil[3], Mallaiah Kenchaveeraiah Swamy[3], Deepa Metgud[4], Sandesh Jogalekar[3], Mahesh Kamate[3], Gauri Divan[5,6], Ruby Gupta[1,2], Dorairaj Prabhakaran[1,2], Nikhil Tandon[7], Usha Ramakrishnan[8], Aryeh D Stein[8]

Abstract

Intake of dietary docosahexaenoic acid (DHA 22:6n-3) is very low among Indian pregnant women. Maternal supplementation during pregnancy and lactation may benefit offspring neurodevelopment. We conducted a double-blind, randomized, placebo-controlled trial to test the effectiveness of supplementing pregnant Indian women (singleton gestation) from ≤20 weeks through 6 months postpartum with 400 mg/d algal DHA compared to placebo on neurodevelopment of their offspring at 12 months. Of 3379 women screened, 1131 were found eligible; 957 were randomized. The primary outcome was infant neurodevelopment at 12 months, assessed using the Development Assessment Scale for Indian Infants (DASII). Both groups were well balanced on sociodemographic variables at baseline. More than 72% of women took >90% of their assigned treatment. Twenty-five serious adverse events (SAEs), none related to the intervention, (DHA group = 16; placebo = 9) were noted. Of 902 live births, 878 were followed up to 12 months; the DASII was administered to 863 infants. At 12 months, the mean development quotient (DQ) scores in the DHA and placebo groups were not statistically significant (96.6 ± 12.2 vs. 97.1 ± 13.0, $p = 0.60$). Supplementing mothers through pregnancy and lactation with 400 mg/d DHA did not impact offspring neurodevelopment at 12 months of age in this setting.

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doi: 10.1093/ajcn/nqaa147.

Micronutrient supplementation of lactating Guatemalan women acutely increases infants' intake of riboflavin, thiamin, pyridoxal, and cobalamin, but not niacin, in a randomized crossover trial

Juliana A Donohue[1,2], Noel W Solomons[3], Daniela Hampel[1,2], Setareh Shahab-Ferdows[1], Mónica N Orozco[4], Lindsay H Allen[1,2]

Abstract

Background: Maternal supplementation during lactation could increase milk B-vitamin concentrations, but little is known about the kinetics of milk vitamin responses.

Objectives: We compared acute effects of maternal lipid-based nutrient supplement (LNS) consumption (n = 22 nutrients, 175%-212% of the RDA intake for the nutrients examined), as a single dose or at spaced intervals during 8 h, on milk concentrations and infant intake from milk of B-vitamins.

Methods: This randomized crossover trial in Quetzaltenango, Guatemala included 26 mother-infant dyads 4-6 mo postpartum who were randomly assigned to receive 3 treatments in a random order: bolus 30-g dose of LNS (Bolus); 3 × 10-g doses of LNS

(Divided); and no LNS (Control), with control meals. Mothers attended three 8-h visits during which infant milk consumption was measured and milk samples were collected at every feed. Infant intake was assessed as $\mathop \sum \nolimits_{i\ = \ 1}^n ({{\rm{milk\ volum}}{{\rm{e}}_{{\rm{feed\ }}n}} \times \ {\rm{nutrient\ concentratio}}{{\rm{n}}_{{\rm{feed}}\ n}})$ over 8 h.
Results: Maternal supplementation with the Bolus or Divided dose increased least-squares mean (95% CI) milk and infant intakes of riboflavin [milk: Bolus: 154.4 (138.2, 172.5) μg · min-1 · mL-1; Control: 84.5 (75.8, 94.3) μg · min-1 · mL-1; infant: Bolus: 64.5 (56.1, 74.3) μg; Control: 34.5 (30.0, 39.6) μg], thiamin [milk: Bolus: 10.9 (10.1, 11.7) μg · min-1 · mL-1; Control: 7.7 (7.2, 8.3) μg · min-1 · mL-1; infant: Bolus: 5.1 (4.4, 6.0) μg; Control: 3.4 (2.9, 4.0) μg], and pyridoxal [milk: Bolus: 90.5 (82.8, 98.9) μg · min-1 · mL-1; Control: 60.8 (55.8, 66.3) μg · min-1 · mL-1; infant: Bolus: 39.4 (33.5, 46.4) μg; Control: 25.0 (21.4, 29.2) μg] (all $P < 0.001$). Only the Bolus dose increased cobalamin in milk [Bolus: 0.054 (0.047, 0.061) μg · min-1 · mL-1; Control: 0.041 (0.035, 0.048) μg · min-1 · mL-1, $P = 0.039$] and infant cobalamin intake [Bolus: 0.023 (0.020, 0.027) μg; Control: 0.015 (0.013, 0.018) μg, $P = 0.001$] compared with Control. Niacin was unaffected.
Conclusions: Maternal supplementation with LNS as a Bolus or Divided dose was similarly effective at increasing milk riboflavin, thiamin, and pyridoxal and infant intakes, whereas only the Bolus dose increased cobalamin. Niacin was unaffected in 8 h.

Am J Clin Nutr. 2021 Apr 6;113(4):884-894.
doi: 10.1093/ajcn/nqaa383.
Impact of nutritional interventions among lactating mothers on the growth of their infants in the first 6 months of life: a randomized controlled trial in Delhi, India
Sunita Taneja[1], Ravi Prakash Upadhyay[1], Ranadip Chowdhury[1], Anura V Kurpad[2], Himani Bhardwaj[1], Tivendra Kumar[1], Pratibha Dwarkanath[2], Beena Bose[2], Sarita Devi[2], Gunjan Kumar[1], Baljeet Kaur[1], Rajiv Bahl[3], Nita Bhandari[1]
Abstract
Background: In lower-middle-income settings, growth faltering in the first 6 mo of life occurs despite exclusive breastfeeding.
Objective: The aim was to test the efficacy of an approach to improve the dietary adequacy of mothers during lactation and thus improve the growth of their infants.
Methods: Eligible mother-infant dyads (infants ≤7 d of age) were randomly assigned to either intervention or control groups. Mothers in the intervention group received snacks that were to be consumed daily, which provided 600 kcal of energy-with 25-30% of energy derived from fats (150-180 kcal) and 13% of energy from protein (80 kcal). Micronutrients were supplemented as daily tablets. We provided counseling on breastfeeding and infant-care practices to mothers in both groups. The primary outcome was attained infant length-for-age z scores (LAZ) at 6 mo of age. Secondary outcomes included exclusive breastfeeding proportion reported by the mother, maternal BMI and midupper arm circumference (MUAC), hemoglobin concentrations in mothers and infants, and the proportion of anemic infants at 6 mo of age.
Results: We enrolled 816 mother-infant dyads. The intervention did not achieve a significant effect on LAZ at 6 mo (adjusted mean difference: 0.09; 95% CI: -0.03, 0.20). Exclusive

breastfeeding at 5 mo was higher (45.1% vs. 34.5%; RR: 1.31; 95% CI: 1.04, 1.64) in the intervention group compared with the controls. There were no significant effects on mean hemoglobin concentration or the proportion of anemic infants at 6 mo of age compared with the control group. We noted significant effects on maternal nutritional status (BMI, MUAC, hemoglobin concentration, and proportion anemic).
Conclusions: Postnatal supplementation of 600 kcal energy, 20 g protein, and multiple micronutrients daily to lactating mothers did not affect infant LAZ at age 6 mo. Such supplementation may improve maternal nutritional status.

Nutrients. 2021 Jan 30;13(2):472.
doi: 10.3390/nu13020472.
Effects of Maternal Nutritional Supplements and Dietary Interventions on Placental Complications: An Umbrella Review, Meta-Analysis and Evidence Map
Mai-Lei Woo Kinshella[1], Shazmeen Omar[1], Kerri Scherbinsky[1,2], Marianne Vidler[1], Laura A Magee[1,3], Peter von Dadelszen[1,3], Sophie E Moore[3,4], Rajavel Elango[2,5,6], The Precise Conceptual Framework Working Group
Abstract
The placenta is a vital, multi-functional organ that acts as an interface between maternal and fetal circulation during pregnancy. Nutritional deficiencies during pregnancy alter placental development and function, leading to adverse pregnancy outcomes, such as pre-eclampsia, infants with small for gestational age and low birthweight, preterm birth, stillbirths and maternal mortality. Maternal nutritional supplementation may help to mitigate the risks, but the evidence base is difficult to navigate. The primary purpose of this umbrella review is to map the evidence on the effects of maternal nutritional supplements and dietary interventions on pregnancy outcomes related to placental disorders and maternal mortality. A systematic search was performed on seven electronic databases, the PROSPERO register and references lists of identified papers. The results were screened in a three-stage process based on title, abstract and full-text by two independent reviewers. Randomized controlled trial meta-analyses on the efficacy of maternal nutritional supplements or dietary interventions were included. There were 91 meta-analyses included, covering 23 types of supplements and three types of dietary interventions. We found evidence that supports supplementary vitamin D and/or calcium, omega-3, multiple micronutrients, lipid-based nutrients, and balanced protein energy in reducing the risks of adverse maternal and fetal health outcomes. However, these findings are limited by poor quality of evidence. Nutrient combinations show promise and support a paradigm shift to maternal dietary balance, rather than single micronutrient deficiencies, to improve maternal and fetal health.

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Gestational age, birth weight and neurocognitive development in adolescents in Tanzania

Nandita Perumal[1], Karim P Manji[2], Anne Marie Darling[3], Rodrick R Kisenge[2], Ingrid Kvestad[4], Mari Hysing[5], David C Belinger[6], Willy Urassa[7], Tor A Strand[8], Christopher P Duggan[9], Wafaie W Fawzi[10], Christopher R Sudfeld[11]

Abstract

Objectives: To investigate the association between gestational age (GA), birthweight, and birthweight adjusted for GA, with domains of neurocognitive development and behavioral problems in adolescents in Tanzania.

Study design: Data from a long-term follow-up of adolescents aged 11 to 15 years born to women previously enrolled in a randomized controlled trial of prenatal multiple micronutrient supplementation in Dar es Salaam, Tanzania, were used. A battery of neurodevelopmental tests were administered to measure adolescent general intelligence, executive function, and behavioral problems. The INTERGROWTH-21st newborn anthropometric standards were used to derive birthweight-for-GA z-scores (BWGAz). We assessed the shape of relationships using restricted cubic splines and estimated the associations of GA, birthweight, and BWGAZ with adolescent development using multivariable linear regressions.

Results: Among adolescents studied (n=421), higher GA (per week), birthweight (per 100 grams), and BWGAz (per SD) were linearly associated with higher intelligence score (adjusted standardized mean difference (aSMD): 0.05 SD (95%CI: 0.01, 0.09), 0.04 SD (95%CI: 0.02, 0.06), and 0.09 SD (95%CI: 0.01, 0.17), respectively). Birthweight and BWGAz, but not GA, were also associated with improved executive function. Low birthweight (<2500 grams) was associated with lower intelligence and executive function scores. Associations between birthweight and executive function were stronger among adolescents born to women with higher education.

Conclusion: Duration of gestation and birthweight were positively associated with adolescent neurodevelopment in Tanzania. These findings suggest that interventions to improve birth outcomes may also benefit adolescent cognitive function.

Maternal mental health

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Impact of maternal mental health interventions on child-related outcomes in low- and middle-income countries: a systematic review and meta-analysis

W A Tol[1,2], M C Greene[2,3], M E Lasater[2], K Le Roch[4], C Bizouerne[4], M Purgato[2,5], M Tomlinson[6,7], C Barbui[5]

Abstract

Aims: Observational studies have shown a relationship between maternal mental health (MMH) and child development, but few studies have evaluated whether MMH interventions improve child-related outcomes, particularly in low- and middle-income countries. The objective of this review is to synthesise findings on the effectiveness of MMH interventions to improve child-related outcomes in low- and middle-income countries (LMICs).

Methods: We searched for randomised controlled trials conducted in LMICs evaluating interventions with a MMH component and reporting children's outcomes. Meta-analysis was performed on outcomes included in at least two trials.

Results: We identified 21 trials with 28 284 mother-child dyads. Most trials were conducted in middle-income countries, evaluating home visiting interventions delivered by general health workers, starting in the third trimester of pregnancy. Only ten trials described acceptable methods for blinding outcome assessors. Four trials showed high risk of bias in at least two of the seven domains assessed in this review. Narrative synthesis showed promising but inconclusive findings for child-related outcomes. Meta-analysis identified a sizeable impact of interventions on exclusive breastfeeding (risk ratio = 1.39, 95% confidence interval (CI): 1.13-1.71, ten trials, N = 4749 mother-child dyads, I2 = 61%) and a small effect on child height-for-age at 6-months (std. mean difference = 0.13, 95% CI: 0.02-0.24, three trials, N = 1388, I2 = 0%). Meta-analyses did not identify intervention benefits for child cognitive and other growth outcomes; however, few trials measured these outcomes.
Conclusions: These findings support the importance of MMH to improve child-related outcomes in LMICs, particularly exclusive breastfeeding. Given, the small number of trials and methodological limitations, more rigorous trials should be conducted.

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Effect of a lay counselor-delivered integrated maternal mental health and early childhood development group-based intervention in Northern Ghana: a cluster-randomized controlled trial

Joy Noel Baumgartner[1,2], Mohammed Ali[3], John A Gallis[2,4], Margaret Lillie[2], Raymond Owusu[3], Safiyatu Abubakr-Bibilazu[3], Haliq Adam[3], Raymond Aborigo[5], Elena McEwan[6], Yunji Zhou[2,4], Eunsoo Timothy Kim[2], Jessica Mackness[2], John Koku Awoonor Williams[7], John Hembling[6]

Abstract

Background: Caregiver mental health is linked to early childhood development, yet more robust evidence of community-based interventions to prevent maternal depression and optimize socio-emotional development of young children is needed. Objectives of this cluster-randomized controlled trial (cRCT), based in Northern Ghana, are to assess the impact of the lay counselor-delivered, group-based Integrated Mothers and Babies Course and Early Childhood Development (iMBC/ECD) program on (1) the mental health of mothers of children under age 2; and (2) the socio-emotional development of their children.
Methods: This cRCT randomized 32 women's groups - 16 received iMBC/ECD content (intervention) and 16 received general health education content (control). Surveys were administered at baseline, immediate post-intervention, and 8-month post-intervention. The primary outcome was maternal depression [Patient Health Questionnaire (PHQ-9)], and the secondary outcome was child's socio-emotional development [Ages and Stages Questionnaire: Social Emotional (ASQ:SE-2)]. Qualitative interviews with 33 stakeholders were also conducted.
Results: In total, 374 participants were enrolled at baseline while pregnant with the index child, 19% endorsing moderate/severe depression. Of these, 266 (71.1%) completed the 8-month post-intervention survey (~19 months post-baseline). There were no significant effects of iMBC/ECD on PHQ-9 and ASQ:SE-2 scores. However, results favored the intervention arm in most cases. iMBC participants were highly satisfied with the program but qualitative feedback from stakeholders indicated some implementation challenges.

Conclusions: This real-world evaluation had null findings; however, post-intervention depression levels were very low in both arms (3%). Future research should examine the potential impact of women's groups on postpartum mental health more broadly with varying content.

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An integrated parenting intervention for maternal depression and child development in a low-resource setting: Cluster randomized controlled trial

Nusrat Husain[1], Tayyeba Kiran[2], Batool Fatima[3], Imran B Chaudhry[1,4], Mina Husain[5], Sadia Shah[1,2], Paul Bassett[6], Nancy Cohen[7], Farhat Jafri[8], Shehla Naeem[9], Zainab Zadeh[2], Chris Roberts[1], Atif Rahman[10], Farooq Naeem[7,11], Muhammad Ishrat Husain[7,11], Nasim Chaudhry[2]

Abstract

Background: Rates of depression among Pakistani mothers are high, leading to poor developmental outcomes in their children. This study tested the effectiveness of a manualized integrated parenting program; Learning through Play Plus (LTP+) for maternal depression in Karachi, Pakistan.

Methods: A cluster randomized control trial conducted from January 2014 to December 2015 across 120 villages in Karachi. A total of 774 depressed mothers aged 18-44 years with children aged 0-30 months old, were included. Villages were randomized to receive LTP+ added to treatment as usual (TAU) or TAU alone. Primary outcomes were severity of maternal depression at 3 and 6 months measured by the Edinburgh Postnatal Depression Scale and child socio-emotional development at 6 months measured by the Ages and Stages Questionnaire (ASQ). Secondary outcomes included maternal anxiety, quality of life, social support, parenting competence, and knowledge about child development.

Results: Mothers in the LTP+ group reported significantly lower depression scores compared to those in the TAU group (6.6 vs. 13.8, effect size [ES]: -7.2; 95% confidence interval [CI]: -8.2, -6.1) at 3 and 6 months (7.2 vs. 12.00; ES: -4.6; 95% CI: -5.9, -3.4). Child socio-emotional development at 6 months was significantly better in the LTP+ group on all domains of the ASQ. There were also statistically significant improvements on all secondary outcomes at 3- and 6-month follow-up.

Conclusion: In low-resource settings like Pakistan, low-cost integrated parenting interventions delivered by lay health workers can provide effective treatment for depressed mothers, leading to improvements in child development.

Health Policy Plan. 2021 May 17;36(4):473-483.
doi: 10.1093/heapol/czaa170.

Effects of a community health worker delivered intervention on maternal depressive symptoms in rural Tanzania

Lilia Bliznashka[1], Aisha K Yousafzai[1], Geofrey Asheri[2], Honorati Masanja[2], Christopher R Sudfeld[1,3]

Abstract

Maternal depression affects one in four women in sub-Saharan Africa, yet evidence on effective and scalable interventions is limited. Our objective was to evaluate the effect of a

community health worker (CHW) delivered home visit responsive stimulation, health and nutrition intervention, and conditional cash transfers (CCTs) for antenatal care and child growth monitoring attendance on maternal depressive symptoms. We conducted a cluster-randomized controlled trial in 12 villages in rural Ifakara, Tanzania (September 2017 to May 2019). Study villages were randomly assigned to one of three arms: (1) CHW, (2) CHW + CCT and (3) Control. Pregnant women and mothers with a child <12 months were enrolled. Maternal depressive symptoms were assessed using a Tanzanian-adapted version of the Hopkins Symptoms Checklist-25 (HSCL-25) after 18 months of follow-up. We used linear mixed-effects models to estimate intervention effects on HSCL-25 scores. Results showed that the CHW intervention significantly reduced HSCL-25 scores as compared with control [unadjusted mean difference (MD) -0.31, 95% confidence interval (CI) -0.47, -0.15]. The CHW + CCT intervention also appeared to lower HSCL-25 scores (MD -0.17, 95% CI -0.33, -0.01), but results were not statistically significant. Our findings showed that a low-intensity CHW-delivered home visit responsive stimulation, health and nutrition intervention, which did not explicitly aim to improve mental health, reduced maternal depressive symptoms, though the precise mechanisms of action remain unknown. CCTs for antenatal care and child growth monitoring appeared to provide limited to no additional benefit. Community-based integrated interventions that broadly consider maternal and child health, development and well-being have the potential to promote maternal mental health in rural Tanzania and similar settings.

Post-natal care and parenting

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Maternal Parenting Electronic Diary in the Context of a Home Visit Intervention for Adolescent Mothers in an Urban Deprived Area of São Paulo, Brazil: Randomized Controlled Trial

Daniel Fatori[#1], Adriana Argeu[#1], Helena Brentani[#1], Anna Chiesa[#2], Lislaine Fracolli[#2], Alicia Matijasevich[#3], Euripedes C Miguel[#1], Guilherme Polanczyk[#1]

Abstract

Background: Pregnancy during adolescence is prevalent in low- and middle-income countries (LMICs), which is associated with various adverse outcomes that can be prevented with home visiting programs. However, testing these interventions in LMICs can be challenging due to limited resources. The use of electronic data collection via smartphones can be an alternative and ideal low-cost method to measure outcomes in an environment with adverse conditions.

Objective: Our study had two objectives: to test the efficacy of a nurse home visiting intervention on maternal parenting and well-being measured by an electronic daily diary (eDiary), and to investigate the compliance rate of the eDiary measurement method.

Methods: We conducted a randomized controlled trial to test the efficacy of Primeiros Laços, a nurse home visiting program, for adolescent mothers living in an urban deprived area of São Paulo, Brazil. A total of 169 pregnant adolescents were assessed for eligibility criteria, 80

of whom were included and randomized to the intervention (n=40) and control group (care as usual, n=40). Primeiros Laços is a home visiting intervention delivered by trained nurses tailored to first-time pregnant adolescents and their children, starting during the first 16 weeks of pregnancy until the child reaches 24 months of age. Participants were assessed by blind interviewers at 8-16 weeks of pregnancy (baseline), 30 weeks of pregnancy, and when the child was 3, 6, and 12 months of age. At 18 months, participants were assessed regarding maternal parenting and parental well-being using a 7-consecutive-day eDiary. The smartphone app was programmed to notify participants every day at 9:00 PM over a period of seven days.
Results: We were able to contact 57/80 (71%) participants (29 from the intervention group and 28 from the control group) when the child was 18 months of age. Forty-eight of the 57 participants (84%) completed at least one day of the eDiary protocol. The daily compliance rate ranged from 49% to 70%. Our analyses showed a significant effect of the intervention on parental well-being (B=0.32, 95% CI [0.06, 0.58], P=.02) and the maternal parenting behavior of the mother telling a story or singing to the child (odds ratio=2.33, 95% CI [1.20, 4.50], P=.01).Our analyses showed a significant effect of the intervention on parental well-being (B=0.32, P=.02) and the maternal parenting behavior of the mother telling a story or singing to the child (odds ratio=2.33, P=.01).
Conclusions: The Primeiros Laços intervention improved maternal parenting and parental well-being, demonstrating its promise for low-income adolescent mothers. The compliance rate of the eDiary assessment showed that it was generally accepted by adolescent mothers with limited resources. Future studies can implement ambulatory assessment in LMICs via smartphones to measure mother and child behaviors.

Family planning and birth spacing

Meningitis and encephalitis

Indian J Pediatr. 2021 Mar;88(3):246-251.
doi: 10.1007/s12098-020-03454-1. Epub 2020 Aug 28.
Seven versus Ten Days Antibiotics Course for Acute Pyogenic Meningitis in Children: A Randomized Controlled Trial
N D Vaswani[1], Nishu Gupta[2], Ravi Yadav[1], Anuradha Nadda[3]
Abstract
Objectives: To compare the efficacy and safety of 7 d vs. 10 d empirical antibiotic therapy in cases of acute pyogenic meningitis in children aged 3 mo to 14 y with rapid initial recovery.
Methods: A total of 96 children aged 3 mo to 14 y with acute pyogenic meningitis were randomized to either 7 d or 10 d therapy on Day 5 of the therapy, if they were in clinical remission and had improving cerebrospinal fluid (CSF) abnormalities. The primary outcome was treatment failure in each group within 10 d of enrolment or relapse of meningitis defined as recurrence of signs and symptoms of meningitis within 2 wk of discharge. Secondary outcome was the presence of sequelae in patient at 30 d and 90 d follow-up post discharge.
Results: Out of 111 screened children, 96 patients completed the trial, 48 in each group. There were 7 treatment failures and relapses each in the group receiving 7 d antibiotics while

6 failures and relapses each were seen in 10 d antibiotics group. There was no statistically significant difference in treatment failure in both the groups [2.1 (-0.12-0.16); p = 0.76]. No deaths or significant adverse effects of the drugs occurred during this study. Four cases of nosocomial sepsis were reported with 2 cases in each group. On subsequent 30 d and 90 d follow-up, no statistically significant difference was found between the two groups regarding frequency of hearing impairment, frequency of hydrocephalus [-2.1 (-0.09-0.13); p = 0.65] and various neurological sequelae [6.2 (-0.06-0.19); p > 0.05].
Conclusions: Short course antibiotic therapy may be adequately effective for treatment of acute pyogenic meningitis beyond neonatal age in children with initial rapid recovery.

Mobile phones and Apps

Medicine (Baltimore). 2021 Mar 12;100(10):e24867.
doi: 10.1097/MD.0000000000024867.
Toward improved adherence: a text message intervention in an human immunodeficiency virus pediatric clinic in Guatemala City
Sergio Alejandro Sánchez[1], Brooke M Ramay[1,2], Jessica Zook[3], Oscar de Leon[2], Ricardo Peralta[4], Julio Juarez[4], Jennifer Cocohoba[3]
Abstract
As access to human immunodeficiency virus treatment expands in Low to Middle Income Countries, it becomes critical to develop and test strategies to improve adherence and ensure efficacy. Text messaging improves adherence to antiretroviral treatment antiretroviral treatment in some patient populations, but data surrounding the use of these tools is sparse in pediatric and adolescent patients in low to middle income countries. We evaluated if a text message intervention can improve antiretroviral treatment adherence while accounting for cell phone access, patterns of use, and willingness to receive text messages.We carried out a cross sectional study to understand willingness of receiving text message reminders, followed by a randomized controlled trial to assess effectiveness of text message intervention.Enrolled participants were randomized to receive standard care with regular clinic visits, or standard care plus short message service reminders. Adherence was measured 3 times during the study period using a 4-day Recall Questionnaire. Outcome was measured based on differences in the average adherence between the intervention and control group at each time point (baseline, 3 months, 6 months).Most respondents were willing to receive text message adherence reminders (81.1%, n = 53). Respondent literacy, travel time to clinic, cell phone access, and patterns of use were significantly associated with willingness. In the randomized trial the intervention group (n = 50) experienced a small but significant mean improvement in adherence over the six-month period (4%, P < .01) whereas the control group (n = 50) did not (mean improvement: 0.8%, P = .64).Text message interventions effectively support antiretroviral adherence in pediatric patients living with human immunodeficiency virus. Studies designed to assess the impact of text messaging interventions must examine local context for cellular phone infrastructure and use and must account for potential loss to follow up when patients miss appointments and study assessments.

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SMS Text Messages for Parents for the Prevention of Child Drowning in Bangladesh: Acceptability Study

Md Mosharaf Hossain[#1], Kulanthayan Mani[#2], Ruhani Mat Min[1]

Abstract

Background: In many cases, greater use is being made of mobile phone text messages as a means of communication between patients and health care providers in countries around the world.

Objective: We studied the use of mobile phones and the factors related to the acceptability of text messages for parents for the prevention of child drowning in Bangladesh.

Methods: From a randomized controlled trial involving 800 parents, 10% (80/800) were selected, and socioeconomic status, mobile phone use, and acceptability of SMS text messages for drowning prevention were measured. Participants with at least one child under 5 years of age were selected from rural areas in Rajshahi District in Bangladesh. Mobile phone-based SMS text messages were sent to the participants. Multivariate regression was used to determine the factors related to the acceptability of text messages for the prevention of child drowning in Bangladesh.

Results: The acceptability of SMS text messages for the prevention of child drowning in Bangladesh was significantly lower among women (odds ratio [OR] 0.50, 95% CI 0.12-1.96, P=.02) than among men, lower for parents older than 30 years (OR 0.17, 95% CI 0.14-1.70, P=.01) compared to parents younger than 30 years, higher among parents who had an education (OR 1.63, 95% CI 1.11-5.80, P=.04) than among illiterate parents, and higher among parents with a monthly household income over 7000 Bangladeshi Taka (approximately US $82.54; OR 1.27, 95% CI 1.06-1.96, P=.05) than among parents whose monthly income was less than 7000 Bangladeshi Taka.

Conclusions: The high percentage of mobile phone use and the acceptability of SMS text messages for parents for the prevention of child drowning are encouraging, in terms of identifying the best strategy for using such technologies, and deserve further evaluation.

Vaccine. 2020 Sep 29;38(42):6600-6608.
doi: 10.1016/j.vaccine.2020.07.075. Epub 2020 Aug 9.

Cost-effectiveness of SMS appointment reminders in increasing vaccination uptake in Lagos, Nigeria: A multi-centered randomized controlled trial

Yoshito Kawakatsu[1], Adefunke Oyeniyi Adesina[2], Nobuhiro Kadoi[3], Hirotsugu Aiga[4]

Abstract

Objective: It is expected that mHealth largely contribute to increasing the coverages of key maternal and child health services. This study aims to estimate the cost-effectiveness of the SMS text reminders in clients' return visits to the health facilities for child vaccinations (incl.

vitamin A supplementations), antenatal care (ANC) and family planning (FP), in urban communities of Lagos, Nigeria.
Methods: A multi-centered randomized control trial was conducted at 33 primary health centers (PHCs) in Lagos, Nigeria. All the clients having visited any of the 33 PHCs for child vaccinations, ANC and FP were randomly assigned either to intervention group or to control group. The participants in the intervention group were sent an SMS text reminder two days before their appointments. Those not having showed up on the appointment dates received an additional SMS text reminder seven days after original appointment dates as defaulter tracing. The primary outcome was whether a client made return visit to PHCs for the upcoming appointments.
Results: Of 12,779 appointments for 9,368 clients during the period of 1stApril to 30thJune 2019, 12,175 were included in the analysis. The return rate for child vaccinations in the intervention group was significantly higher ($p < 0.001$) by 4.8% - 6.0% than that in the control group, consistently across all the five different timings (on time as scheduled, and by 7 days, 14 days, 30 days, and 3 months after appointment dates). No significant difference between the two groups was detected in the increase in return rates for ANC and FP services. The incremental recurrent cost was estimated at 7.90 US Dollars per return case.
Conclusion: SMS text reminders led to a significant increase in the number of return visits for child vaccinations, Lagos, Nigeria, while no significant increase in return visits was confirmed for ANC and FP appointments.

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doi: 10.2196/27603.
Effect of Mobile Phone Text Message Reminders on the Completion and Timely Receipt of Routine Childhood Vaccinations: Superiority Randomized Controlled Trial in Northwest Ethiopia
Zeleke Abebaw Mekonnen[1], Kassahun Alemu Gelaye[2], Martin Were[3], Binyam Tilahun[1]
Abstract
Background: Nonattendance at vaccination appointments is a big challenge for health workers as it is difficult to track routine vaccination schedules. In Ethiopia, 3 out of 10 children have incomplete vaccination and the timely receipt of the recommended vaccines is low. Thus, innovative strategies are required to reach the last mile where mobile technology can be effectively utilized to achieve better compliance. Despite this promising technology, little is known about the role of text message-based mobile health interventions in improving the complete and timely receipt of routine childhood vaccinations in Ethiopia.
Objective: This trial aimed to determine the effect of mobile phone text message reminders on the completion and timely receipt of routine childhood vaccinations in northwest Ethiopia.
Methods: A two-arm, parallel, superiority randomized controlled trial was conducted in 9 health facilities in northwest Ethiopia. A sample size of 434 mother-infant pairs was considered in this trial. Randomization was applied in selected health facilities during enrollment with a 1:1 allocation ratio by using sealed and opaque envelopes. Participants assigned to the intervention group received mobile phone text message reminders one day before the scheduled vaccination visits. Owing to the nature of the intervention, blinding of participants was not possible. Primary outcomes of full and timely completion of

vaccinations were measured objectively at 12 months. A two-sample test of proportion and log-binomial regression analyses were used to compare the outcomes between the study groups. A modified intention-to-treat analysis approach was applied and a one-tailed test was reported, considering the superiority design of the trial.
Results: A total of 426 participants were included for the analysis. We found that a higher proportion of infants in the intervention group received Penta-3 (204/213, 95.8% vs 185/213, 86.9%, respectively; P<.001), measles (195/213, 91.5% vs 169/213, 79.3%, respectively; P<.001), and full vaccination (176/213, 82.6% vs 151/213, 70.9%, respectively; P=.002; risk ratio 1.17, 95% lower CI 1.07) compared to infants in the usual care group. Similarly, a higher proportion of infants in the intervention group received Penta-3 (181/204, 88.7% vs 128/185, 69.2%, respectively; P<.001), measles (170/195, 87.1% vs 116/169, 68.6%, respectively; P<.001), and all scheduled vaccinations (135/213, 63.3% vs 85/213, 39.9%, respectively; P<.001; risk ratio 1.59, 95% lower CI 1.35) on time compared to infants in the usual care group. Of the automatically sent 852 mobile phone text messages, 764 (89.7%) were delivered successfully to the participants.
Conclusions: Mobile phone text message reminders significantly improved complete and timely receipt of all recommended vaccines. Besides, they had a significant effect in improving the timely receipt of specific vaccines. Thus, text message reminders can be used to supplement the routine immunization program in resource-limited settings. Considering different contexts, studies on the implementation challenges of mobile health interventions are recommended.

JMIR Mhealth Uhealth. 2020 Oct 14;8(10):e17066.
doi: 10.2196/17066.
Costing and Cost-Effectiveness of a Mobile Health Intervention (ImTeCHO) in Improving Infant Mortality in Tribal Areas of Gujarat, India: Cluster Randomized Controlled Trial
Dhiren Modi[1], Somen Saha[2], Prakash Vaghela[3], Kapilkumar Dave[1], Ankit Anand, Shrey Desai[1], Pankaj Shah[1]
Abstract
Background: During 2013, a mobile health (mHealth) program, Innovative Mobile Technology for Community Health Operation (ImTeCHO), was launched in predominantly tribal and rural communities of Gujarat, India. ImTeCHO was developed as a job aid for Accredited Social Health Activists (ASHAs) and staff of primary health centers to increase coverage of maternal, neonatal, and child health care.
Objective: In this study, we assessed the incremental cost per life-years saved as a result of the ImTeCHO intervention as compared to routine maternal, neonatal, and child health care programs.
Methods: A two-arm, parallel, stratified cluster randomized trial with 11 clusters (primary health centers) randomly allocated to the intervention (280 ASHAs, n=2,34,134) and control (281 ASHAs, n=2,42,809) arms was initiated in 2015 in a predominantly tribal and rural community of Gujarat. A system of surveillance assessed all live births and infant deaths in the intervention and control areas. All costs, including those required during the start-up and implementation phases, were estimated from a program perspective. Incremental cost-effectiveness ratios were estimated by dividing the incremental cost of the intervention with the number of deaths averted to estimate the cost per infant death averted. This was further

analyzed to estimate the cost per life-years saved for the purpose of comparability. Sensitivity analysis was undertaken to account for parameter uncertainties.
Results: Out of a total of 5754 live births (3014 in the intervention arm, 2740 in the control arm) reported in the study area, per protocol analysis showed that the implementation of ImTeCHO resulted in saving 11 infant deaths per 1000 live births in the study area at an annual incremental cost of US $163,841, which is equivalent to US $54,360 per 1000 live births. Overall, ImTeCHO is a cost-effective intervention from a program perspective at an incremental cost of US $74 per life-years saved or US $5057 per death averted. In a realistic environment with district scale-up, the program is expected to become even more cost-effective.
Conclusions: Overall, the findings of our study strongly suggest that the mHealth intervention as part of the ImTeCHO program is cost-effective and should be considered for replication elsewhere in India.

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Effectiveness of Mobile Phone-Based Support on Exclusive Breastfeeding and Infant Growth in Nigeria: A Randomized Controlled Trial

Daprim S Ogaji[1,2], Adaku O Arthur[3], Innocent George[4]

Abstract
Background: This study examined whether mobile phone-based support improve the rates, duration of exclusive breastfeeding (EBF) as well as infant growth patterns in Nigeria.
Methods: A 6-month prospective randomized controlled trial with 75 participants assigned to receive 'usual care' or 'mobile phone-based support in addition to usual care' EBF rates and duration as well as anthropometric measurements of infants before and after intervention were compared using proportions and mean differences.
Results: Attrition rates of 10.7% and 14.7% were observed in the intervention and control groups, respectively. Treatment groups were identical in all baseline characteristics and participants in the intervention group showed a slower rate of decline in the practice of EBF. The mean difference of 0.6 months (95% confidence interval: -0.22, 1.42) in EBF duration between intervention and control groups was not statistically significant ($t = 1.45$; $p = 0.149$). Similarly, the difference in the EBF rates at the 6th month for the intervention (55.2%) and control (46.8%) groups was not statistically significant ($\chi 2 = 0.623$; $p = 0.430$). Although the intervention group had significantly higher mean weight ($p = 0.030$) and length ($p = 0.044$) at the 6th month, the difference in the gain in weight and length of these infants over the period was only significant for the weight ($p = 0.044$). Although the incidence of adverse clinical nutritional status was more in the control group, these differences were not statistically significant.
Conclusion: Mobile phone-based intervention has positive effects on the rate and duration of EBF as well as the growth of young infants. Sustaining this simple and cheap technology will improve infant wellbeing especially in resource-constrained settings.

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doi: 10.2196/20356.

Social and Behavior Change Communication Interventions Delivered Face-to-Face and by a Mobile Phone to Strengthen Vaccination Uptake and Improve Child Health in Rural India: Randomized Pilot Study

Mira Johri[1,2], Dinesh Chandra[3], Karna Georges Kone[1,4], Marie-Pierre Sylvestre[1,5], Alok K Mathur[6], Sam Harper[7,8], Arijit Nandi[7,9]

Abstract

Background: In resource-poor settings, lack of awareness and low demand for services constitute important barriers to expanding the coverage of effective interventions. In India, childhood immunization is a priority health strategy with suboptimal uptake.

Objective: To assess study feasibility and key implementation outcomes for the Tika Vaani model, a new approach to educate and empower beneficiaries to improve immunization and child health.

Methods: A cluster-randomized pilot trial with a 1:1 allocation ratio was conducted in rural Uttar Pradesh, India, from January to September 2018. Villages were randomly assigned to either the intervention or control group. In each participating village, surveyors conducted a complete enumeration to identify eligible households and requested participation before randomization. Interventions were designed through formative research using a social marketing approach and delivered over 3 months using strategies adapted to disadvantaged populations: (1) mobile health (mHealth): entertaining educational audio capsules (edutainment) and voice immunization reminders via mobile phone and (2) face-to-face: community mobilization activities, including 3 small group meetings offered to each participant. The control group received usual services. The main outcomes were prespecified criteria for feasibility of the main study (recruitment, randomization, retention, contamination, and adoption). Secondary endpoints tested equity of coverage and changes in intermediate outcomes. Statistical methods included descriptive statistics to assess feasibility, penalized logistic regression and ordered logistic regression to assess coverage, and generalized estimating equation models to assess changes in intermediate outcomes.

Results: All villages consented to participate. Gaps in administrative data hampered recruitment; 14.0% (79/565) of recorded households were nonresident. Only 1.4% (8/565) of households did not consent. A total of 387 households (184 intervention and 203 control) with children aged 0 to 12 months in 26 villages (13 intervention and 13 control) were included and randomized. The end line survey occurred during the flood season; 17.6% (68/387) of the households were absent. Contamination was less than 1%. Participation in one or more interventions was 94.0% (173/184), 78.3% (144/184) for the face-to-face strategy, and 67.4% (124/184) for the mHealth strategy. Determinants including place of residence, mobile phone access, education, and female empowerment shaped intervention use; factors operated differently for face-to-face and mHealth strategies. For 11 of 13 intermediate outcomes, regression results showed significantly higher basic health knowledge among the intervention group, supporting hypothesized causal mechanisms.

Conclusions: A future trial of a new intervention model is feasible. The interventions could strengthen the delivery of immunization and universal primary health care. Social and behavior change communication via mobile phones proved viable and contributed to standardization and scalability. Face-to-face interactions remain necessary to achieve equity and reach, suggesting the need for ongoing health system strengthening to accompany the introduction of communication technologies.

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Effects of Smartphone-Based Interventions on Physical Activity in Children and Adolescents: Systematic Review and Meta-analysis

Zihao He[#1], Hua Wu[#2], Fengyu Yu[1], Jinmei Fu[3], Shunli Sun[3], Ting Huang[1], Runze Wang[1], Delong Chen[1], Guanggao Zhao[1], Minghui Quan[4]

Abstract

Background: About 70% of children and adolescents worldwide do not meet the recommended level of physical activity (PA), which is closely associated with physical, psychological, and cognitive well-being. Nowadays, the use of technologies to change PA is of interest due to the need for novel, more effective intervention approaches. The previous meta-analyses have examined smartphone-based interventions and their impact on PA in adults, but evidence in children and adolescents still needs further research.

Objective: This systematic review and meta-analysis aimed to determine the effectiveness of smartphone-based interventions for improving PA in children and adolescents.

Methods: Five electronic databases (PubMed, Web of Science, OVID, Scopus, and the China National Knowledge Infrastructure) were searched up to June 29, 2020. Randomized controlled trials with a control group that examine the effect of smartphone interventions on PA among children and adolescents were included. Bias risks were assessed using the Cochrane collaboration tool. Meta-analysis was performed to assess the pooled effect on PA using a random effects model. Subgroup analyses were conducted to examine the potential modifying effects of different factors (eg, types of intervention, intervention duration, age, measurement, study quality).

Results: A total of 9 studies were included in this review, including 4 mobile app interventions, 3 SMS text messaging interventions, and 2 app + SMS text messaging interventions. In general, the risk of bias of included studies was low. Compared with the control group, the use of smartphone intervention significantly improved PA (standardized mean difference [SMD] 0.44, 95% CI 0.11-0.77, P=.009), especially for total PA (TPA; weighted mean difference [WMD] 32.35, 95% CI 10.36-54.33, P=.004) and daily steps (WMD 1185, 95% CI 303-2068, P=.008), but not for moderate-to-vigorous PA (WMD 3.91, 95% CI -1.99 to 9.81, P=.19). High statistical heterogeneity was detected (I^2=73.9%, P<.001) for PA. Meta-regression showed that duration (β=-.08, 95% CI -0.15 to -0.01, n=16) was a potential factor for high heterogeneity. The results of subgroup analyses indicated that app intervention (SMD 0.76, 95% CI 0.23-1.30, P=.005), children (SMD 0.64, 95% CI 0.10-1.18, P=.02), "≤8 weeks" (SMD 0.76, 95% CI 0.23-1.30, P=.005), objective measurement (SMD 0.50, 95% CI 0.09-0.91, P=.02), and low risk of bias (SMD 0.96, 95% CI 0.38-1.54, P=.001) can significantly improve PA.

Conclusions: The evidence of meta-analysis shows that smartphone-based intervention may be a promising strategy to increase TPA and steps in children and adolescents. Currently, app intervention may be a more effective strategy among smartphone intervention technologies. To extend the promise of smartphone intervention, the future needs to design comparative trials among different smartphone technologies.

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Effectiveness of E-Learning Program in Preventing WP Smoking in Adolescent Females in West of Iran by Applying Prototype-Willingness Model: A Randomized Controlled Trial

Saeed Bashirian[1], Majid Barati[1], Manoochehr Karami[2], Behrooz Hamzeh[3], Elahe Ezati[4]

Abstract

Background: Given the increasing trend of Water pipe (WP) smoking in adolescent females, it is necessary to use effective educational strategies in preventing WP smoking in developing countries. We aimed to determine effectiveness of e-learning program in preventing WP smoking in adolescent females west of Iran using prototype-willingness model.

Study design: A randomized controlled trial.

Methods: This study was performed on 221 adolescent females in Kermanshah City, Iran during 2019-2020. Multistage random sampling was used. Data collection tool included a researcher-made questionnaire based on prototype-willingness model. E-learning-based intervention program included 5 training sessions. Participants were followed up for 3 months after the intervention. The data were analyzed using SPSS software.

Results: The mean scores of attitude, subjective norms, prototype, intention, and behavioral willingness structures were similar in both experimental and control groups before the educational intervention. However, after educational interventions, mean scores of structures of positive attitude towards WP, subjective norms about WP smoking, positive prototype about WP smokers, intention, and behavioral willingness towards WP smoking were decreased in the experimental group. Moreover, frequency of WP smoking was decreased in the experimental group compared to the control group after the educational intervention (P=0.003).

Conclusion: The use of e-learning-based interventions is an educational strategy for reducing WP smoking in adolescent females.

Neurological disease and neurodevelopmental conditions

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Effectiveness of a technology-assisted, family volunteers delivered, brief, multicomponent parents' skills training intervention for children with developmental disorders in rural Pakistan: a cluster randomized controlled trial

Syed Usman Hamdani[1 2 3], Zill-E- Huma[4 5], Nadia Suleman[5], Parveen Akhtar[5], Huma Nazir[5], Aqsa Masood[5], Mahjabeen Tariq[5], Ahmareen Koukab[5], Erica Salomone[6 7], Laura Pacione[6 8], Felicity Brown[9 10], Stephanie Shire[11], Siham Sikander[4], Chiara Servili[6], Duolao Wang[12], Fareed Aslam Minhas[13], Atif Rahman[4]

Abstract

Background: Globally, there is a large documented gap between needs of families and children with developmental disorders and available services. We adapted the World Health Organization's mental health Gap-Intervention Guidelines (mhGAP-IG) developmental disorders module into a tablet-based android application to train caregivers of children with

developmental disorders. We aimed to evaluate the effectiveness of this technology-assisted, family volunteers delivered, parents' skills training intervention to improve functioning in children with developmental disorders in a rural community of Rawalpindi, Pakistan.
Methods: In a single-blinded, cluster randomized controlled trial, 30 clusters were randomised (1:1 ratio) to intervention (n = 15) or enhanced treatment as usual (ETAU) arm (n = 15). After screening, 540 children (18 participants per cluster) aged 2-12 years, with developmental disorders and their primary caregivers were recruited into the trial. Primary outcome was child's functioning, measured by Childhood Disability Assessment Schedule for Developmental Disorders (DD-CDAS) at 6-months post-intervention. Secondary outcomes were parents' health related quality of life, caregiver-child joint engagement, socio-emotional well-being of children, family empowerment and stigmatizing experiences. Intention-to-treat analyses were done using mixed-models adjusted for covariates and clusters.
Results: At 6-months post-intervention, no statistically significant mean difference was observed on DD-CDAS between intervention and ETAU (mean [SD], 47.65 [26.94] vs. 48.72 [28.37], Adjusted Mean Difference (AMD), - 2.63; 95% CI - 6.50 to 1.24). However, parents in the intervention arm, compared to ETAU reported improved health related quality of life (mean [SD] 65.56 [23.25] vs. 62.17 [22.63], AMD 5.28; 95% CI 0.44 to 10.11). The results were non-significant for other secondary outcomes.
Conclusions: In the relatively short intervention period of 6 months, no improvement in child functioning was observed; but, there were significant improvements in caregivers' health related quality of life. Further trials with a longer follow-up are recommended to evaluate the impact of intervention. Trial registration Clinicaltrials.gov, NCT02792894. Registered April 4, 2016, https://clinicaltrials.gov/ct2/show/NCT02792894.

Indian Pediatr. 2021 May 28;S097475591600332.
Add-on Home-Centred Activity-Based Therapy vs Conventional Physiotherapy in Improving Walking Ability at 6-Months in Children with Diplegic Cerebral Palsy: A Randomized Controlled Trial
Jyotindra Narayan Goswami[1], Naveen Sankhyan[1], Pratibha Singhi[2]
Abstract
Background: Institutional physiotherapy as a standard of care for management of cerebral palsy (CP) has certain shortcomings, especially in resource-constrained settings. This is a proof-of-concept trial to evaluate the efficacy of individualized home-centered activity-based therapy in children with spastic diplegic CP.
Design: Randomized controlled trial (open-label).
Settings: Tertiary-care hospital with pediatric neurology services (July 2014 to July 2016).
Participants: Consecutive sample of 59 children (5-12yrs) with spastic diplegic CP (Gross Motor Function Classification System scores II - III) without fixed lower-limb contractures, illnesses impeding physiotherapy or history of recent botulinum toxin injection/surgery were recruited.
Procedure: Children were randomized to Intervention or Control arms. Their 6-minute-walk Test (6MWT) scoring and clinical examination were performed at baseline, 3 and 6 months. Children in Intervention Arm (n=30) were prescribed parent-supervised home-centered

activity-based therapy (walking, standing, squatting, climbing up/downstairs, kicking a ball, dancing, riding a tricycle/bicycle) in addition to their institutional physiotherapy. Children in Control Arm (n=29) were prescribed ongoing institutional physiotherapy alone. Logbooks, home videos and telephonic follow-ups were used to ensure compliance.
Main outcome measures: Comparison of the mean change in 6MWT scores at 6 months (from baseline) between the two groups.
Results: Median (IQR) change in 6MWT scores at 6 months (from baseline) in the Intervention and Control arms were 3.5 (-5.3, 9) m and 3 (-7.8, 6.3) m.
Conclusion: Adjunct home-centered activity-based therapy was safe and feasible, but did not result in appreciable gains over 6 months.

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doi: 10.23736/S1973-9087.21.06802-7. Online ahead of print.

Effect of oral sensorimotor stimulation on oropharyngeal dysphagia in children with spastic cerebral palsy: a randomized controlled trial

Amira M Abd-Elmonem[1], Sara S Saad-Eldien[2], Walaa A El-Nabie[3]

Abstract
Background: Children with cerebral palsy show various degrees of dysphagia causing late development of oral motor skills.
Aim: To investigate effect of oral sensorimotor stimulation on oropharyngeal dysphagia in children with spastic quadriplegia.
Design: This was a double-masked, randomized controlled clinical trial.
Setting: Out-patient Clinics of Faculty of Physical Therapy, Cairo University and Modern University of Technology and information.
Population: A convenient sample of 71 children age ranged from 12 to 48 months diagnosed with spastic quadriplegia, were randomly assigned into two groups.
Methods: Children in the control group received 90 minutes conventional physical therapy training five times/week for 4 successive months while those in the experimental group received 20 minutes of oral sensorimotor stimulation before the same program as in control group for 60 minutes. Oral motor function, body weight, segmental trunk control and gross motor function were assessed at base-line and after completing treatment.
Results: In total, 64 (experimental n=32, control n=32) children completed treatment and data collection. The baseline assessment showed non-significant difference regarding all measured variables while with-in group comparison showed significant improvement in the two groups. The post-treatment comparisons revealed significant difference the oral motor function and physical growth in favor of the experimental group ($p < 0.05$). Finally, there was non-significant difference regarding segmental trunk control and gross motor function ($p > 0.05$).
Conclusions: Oral sensorimotor stimulation has the capability to improve feeding in children with spastic cerebral palsy diagnosed with oropharyngeal dysphagia.
Clinical rehabilitayion impact: OSMS has effect on some of the essential oral motor skills that contribute toward the improvement of feeding performance in children with spastic CP.

The results of our study offer remarkable clinical importance for the children and their families.

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doi: 10.4103/jpn.JPN_88_19. Epub 2020 Nov 6.

Dynamic Surface Exercise Training in Improving Trunk Control and Gross Motor Functions among Children with Quadriplegic Cerebral Palsy: A Single Center, Randomized Controlled Trial

Sravan Reddy[1], Gandhi Karunanithi Balaji[1]

Abstract

Background: Dynamic surface provides proprioceptive and vestibular feedback with optimal level of arousal. The activities on unstable environment have greater sensorimotor experiences. There is a lack of evidence examining the benefits of dynamic surface exercise training (DSET) among the children with spastic quadriplegic cerebral palsy (CP).

Aim: The aim of the study was to analyze the effect of dynamic surface exercises on trunk control and gross motor functions in children with quadriplegic CP.

Materials and methods: A total of 30 children with spastic quadriplegic CP with Gross Motor Function Classification System of levels III and IV were recruited by the simple random sampling method (random number generator) to participate in this randomized controlled study. Recruited children were randomly divided into two groups, DSET group and standard physiotherapy training group. Both the groups received active training program lasting for 60 min, 4 days/week for 6 weeks. Gross Motor Function Measure (GMFM)-88 and Pediatric Balance Scale (PBS) scores were recorded at baseline, and at the end of 6-week post-intervention.

Results: Total 30 children with quadriplegic CP with mean age 6.64 ± 2.15 years in experimental group and 6.50 ±1.59 years in control group participated in the study. Experimental group showed a significant difference for GMFM and PBS scores between pre- and post-intervention with $P < 0.005$. A significant difference was observed in GMFM scores between experimental and control group with $P < 0.005$.

Conclusion: Six-week dynamic surface exercise therapy along with standard physiotherapy was effective in improving trunk control and gross motor function performance among children with spastic quadriplegic CP aged 6-12 years.

Somatosens Mot Res. 2021 Jun;38(2):117-126.
doi: 10.1080/08990220.2021.1876016. Epub 2021 Mar 3.

Randomised trial of virtual reality gaming and physiotherapy on balance, gross motor performance and daily functions among children with bilateral spastic cerebral palsy

Krishna Kumari Jha[1], Gandhi Balaji Karunanithi[1], A Sahana[1], Suruliraj Karthikbabu[2]

Abstract

Background: Balance issues and poor gross motor function affect the daily needs of children with cerebral palsy.

Purpose: The study objective was to examine the effects of virtual reality gaming and physiotherapy on balance, gross motor performance and daily functioning among children with bilateral spastic cerebral palsy.
Method: Thirty-eight children with bilateral spastic cerebral palsy aged 6-12 years with GMFCS- level II-III, Manual Ability Classification System level I-III participated in this randomized controlled trial. The experimental group performed virtual reality games and physiotherapy, while the control group underwent physiotherapy alone. The exercise intensity was 60 minutes session a day, 4-days a week for 6-weeks. Paediatric Balance Scale (PBS), Kids-Mini-Balance Evaluation System Test (Kids-Mini-BESTest), Gross Motor Function Measure-88 (GMFM-88), and Wee-Functional Independence Measure (WeeFIM) were the outcome measures collected at baseline, 6-week post-training and 2-months follow-up.
Results: The time by group interaction of repeated measures ANOVA revealed no statistical significance for all the outcome measures except Kids-Mini-BESTest ($p < 0.05$). The PBS and, Kids-Mini-BESTest improved by a mean (standard deviation) score of 5.1(1.7) and 8.7(2.8) points, respectively in the experimental group as compared to control group [3.4(1.6) and 5.8(2.5) points]. These gains remained at follow-up ($p < 0.001$).
Conclusion: Combined virtual reality gaming and physiotherapy is not superior over physiotherapy alone in improving the gross motor performance and daily functioning among children with bilateral spastic cerebral palsy. Virtual gaming, along with physiotherapy, appears to be beneficial in their balance capacity, warranting further trials to investigate the same in children with GMFCS level-III.

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Parent mediated intervention programmes for children and adolescents with neurodevelopmental disorders in South Asia: A systematic review

Kamrun Nahar Koly[1], Susanne P Martin-Herz[2], Md Saimul Islam[1], Nusrat Sharmin[1,3], Hannah Blencowe[4], Aliya Naheed[1]

Abstract

Objective: Parent-mediated programmes have been found to be cost effective for addressing the needs of the children and adolescents with Neurodevelopmental Disorders (NDD) in high-income countries. We explored the impact of parent-mediated intervention programmes in South Asia, where the burden of NDD is high.
Methods: A systematic review was conducted using the following databases; PUBMED, MEDLINE, PsycINFO, Google Scholar and Web of Science. Predefined MeSH terms were used, and articles were included if published prior to January 2020. Two independent researchers screened the articles and reviewed data.
Outcomes measures: The review included studies that targeted children and adolescents between 1 and 18 years of age diagnosed with any of four specific NDDs that are commonly reported in South Asia; Autism Spectrum Disorder (ASD), Intellectual Disability (ID), Attention Deficit Hyperactivity Disorder (ADHD) and Cerebral Palsy (CP). Studies that reported on parent or child outcomes, parent-child interaction, parent knowledge of NDDs, or child activities of daily living were included for full text review.
Results: A total of 1585 research articles were retrieved and 23 studies met inclusion criteria, including 9 Randomized Controlled Trials and 14 pre-post intervention studies. Of these,

seventeen studies reported effectiveness, and six studies reported feasibility and acceptability of the parent-mediated interventions. Three studies demonstrated improved parent-child interaction, three studies demonstrated improved child communication initiations, five studies reported improved social and communication skills in children, four studies demonstrated improved parental knowledge about how to teach their children, and four studies reported improved motor and cognitive skills, social skills, language development, learning ability, or academic performance in children.
Conclusion: This systematic review of 23 studies demonstrated improvements in parent and child skills following parent-mediated intervention in South Asia. Additional evaluations of locally customized parent-mediated programmes are needed to support development of feasible interventions for South Asian countries.

Newborn care

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doi: 10.1136/bmjgh-2017-000680.
Effect of home-based newborn care on neonatal and infant mortality: a cluster randomised trial in India
Reeta Rasaily[1], N C Saxena[2], Sushma Pandey[3], Bishan S Garg[4], Saraswati Swain[5], Sharad D Iyengar[6], Vinita Das[7], Sheela Sinha[3], Subodh Gupta[4], Anju Sinha[2], Shiv Kumar[2], Arvind Pandey[8], Ravindra Mohan Pandey[9], Harshpal Singh Sachdev[10], Mari Jeeva Sankar[9], Siddarth Ramji[11], Vinod K Paul[9], Abhay T Bang[12], ICMR-HBMYI Study Group; ICMR -HBMYI Study Group
Abstract
Background: Home-based newborn care has been found to reduce neonatal mortality in rural areas. Study evaluated effectiveness of home-based care delivered by specially recruited newborn care workers- Shishu Rakshak (SR) and existing workers- anganwadi workers (AWW) in reducing neonatal and infant mortality rates.
Methods: This three-arm, community-based, cluster randomised trial was conducted in five districts in India. Intervention package consisted of pregnancy surveillance, health education, care at birth, care of normal/low birthweight neonates, identification and treatment of sick neonates and young infants using oral and injectable antibiotics and community mobilisation. The package was similar in both intervention arms-SR and AWW; difference being healthcare provider. The control arm received routine health services from the existing health system. Primary outcomes were neonatal and young infant mortality rates at 'endline' period (2008-2009) assessed by an independent team from January to April 2010 in the study clusters.
Findings: A total of 6623, 6852 and 5898 births occurred in the SR, AWW and control arms, respectively, during the endline period; the proportion of facility births were 69.0%, 64.4% and 70.6% in the three arms. Baseline mortality rates were comparable in three arms. During the endline period, the risk of neonatal mortality was 25% lower in the SR arm (adjusted OR 0.75, 95% CI 0.57 to 0.99); the risks of early neonatal mortality, young infant mortality and infant mortality were also lower by 32%, 27%, and 33%, respectively. The risks of neonatal, early neonatal, young infant, infant mortality in the AWW arm were not different from that of the control arm.

Interpretation: Home-based care is effective in reducing neonatal and infant mortality rates, when delivered by a dedicated worker, even in settings with high rates of facility births.

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Evaluation of a package of continuum of care interventions for improved maternal, newborn, and child health outcomes and service coverage in Ghana: A cluster-randomized trial

Akira Shibanuma[1], Evelyn Korkor Ansah[2 3], Kimiyo Kikuchi[1 4], Francis Yeji[5], Sumiyo Okawa[1 6], Charlotte Tawiah[7], Keiko Nanishi[1], Sheila Addei[8], John Williams[8], Kwaku Poku Asante[7], Abraham Oduro[5], Seth Owusu-Agyei[3 7], Margaret Gyapong[3 8], Gloria Quansah Asare[2], Junko Yasuoka[1 9], Abraham Hodgson[2], Masamine Jimba[1], Ghana EMBRACE Implementation Research Project Team

Abstract

Background: In low- and middle-income countries (LMICs), the continuum of care (CoC) for maternal, newborn, and child health (MNCH) is not always complete. This study aimed to evaluate the effectiveness of an integrated package of CoC interventions on the CoC completion, morbidity, and mortality outcomes of woman-child pairs in Ghana.

Methods and findings: This cluster-randomized controlled trial (ISRCTN: 90618993) was conducted at 3 Health and Demographic Surveillance System (HDSS) sites in Ghana. The primary outcome was CoC completion by a woman-child pair, defined as receiving antenatal care (ANC) 4 times or more, delivery assistance from a skilled birth attendant (SBA), and postnatal care (PNC) 3 times or more. Other outcomes were the morbidity and mortality of women and children. Women received a package of interventions and routine services at health facilities (October 2014 to December 2015). The package comprised providing a CoC card for women, CoC orientation for health workers, and offering women with 24-hour stay at a health facility or a home visit within 48 hours after delivery. In the control arm, women received routine services only. Eligibility criteria were as follows: women who gave birth or had a stillbirth from September 1, 2012 to September 30, 2014 (before the trial period), from October 1, 2014 to December 31, 2015 (during the trial period), or from January 1, 2016 to December 31, 2016 (after the trial period). Health service and morbidity outcomes were assessed before and during the trial periods through face-to-face interviews. Mortality was assessed using demographic surveillance data for the 3 periods above. Mixed-effects logistic regression models were used to evaluate the effectiveness as difference in differences (DiD). For health service and morbidity outcomes, 2,970 woman-child pairs were assessed: 1,480 from the baseline survey and 1,490 from the follow-up survey. Additionally, 33,819 cases were assessed for perinatal mortality, 33,322 for neonatal mortality, and 39,205 for maternal mortality. The intervention arm had higher proportions of completed CoC (410/870 [47.1%]) than the control arm (246/620 [39.7%]; adjusted odds ratio [AOR] for DiD = 1.77; 95% confidence interval [CI]: 1.08 to 2.92; p = 0.024). Maternal complications that required hospitalization during pregnancy were lower in the intervention (95/870 [10.9%]) than in the control arm (83/620 [13.4%]) (AOR for DiD = 0.49; 95% CI: 0.29 to 0.83; p = 0.008). Maternal mortality was 8/6,163 live births (intervention arm) and 4/4,068 live births during the trial period (AOR for DiD = 1.60; 95% CI: 0.40 to 6.34; p = 0.507) and 1/4,626 (intervention arm) and 9/3,937 (control arm) after the trial period (AOR for DiD = 0.11; 95% CI: 0.11 to 1.00; p = 0.050).

Perinatal and neonatal mortality was not significantly reduced. As this study was conducted in a real-world setting, possible limitations included differences in the type and scale of health facilities and the size of subdistricts, contamination for intervention effectiveness due to the geographic proximity of the arms, and insufficient number of cases for the mortality assessment.
Conclusions: This study found that an integrated package of CoC interventions increased CoC completion and decreased maternal complications requiring hospitalization during pregnancy and maternal mortality after the trial period. It did not find evidence of reduced perinatal and neonatal mortality.

Trop Med Health. 2020 Nov 4;48(1):89.doi: 10.1186/s41182-020-00275-y.
Prevalence and factors associated with neonatal hypoglycemia in Northern Uganda: a community-based cross-sectional study
David Mukunya[1 2 3], Beatrice Odongkara[4 5], Thereza Piloya[6], Victoria Nankabirwa[7 8], Vincentina Achora[9], Charles Batte[10], James Ditai[11], Thorkild Tylleskar[7], Grace Ndeezi[6], Sarah Kiguli[6], James K Tumwine[6]
Abstract
Background: Neonatal hypoglycemia is the most common endocrine abnormality in children, which is associated with increased morbidity and mortality. The burden and risk factors of neonatal hypoglycemia in rural communities in sub-Saharan Africa are unknown.
Objective: To determine the prevalence and risk factors for neonatal hypoglycemia in Lira District, Northern Uganda.
Methods: This was a community-based cross-sectional study, nested in a cluster randomized controlled trial designed to promote health facility births and newborn care practices in Lira District, Northern Uganda. This study recruited neonates born to mothers in the parent study. Random blood glucose was measured using an On Call® Plus glucometer (ACON Laboratories, Inc., 10125 Mesa Road, San Diego, CA, USA). We defined hypoglycemia as a blood glucose of < 47 mg/dl. To determine the factors associated with neonatal hypoglycemia, a multivariable linear regression mixed-effects model was used.
Results: We examined 1416 participants of mean age 3.1 days (standard deviation (SD) 2.1) and mean weight of 3.2 kg (SD 0.5). The mean neonatal blood glucose level was 81.6 mg/dl (SD 16.8). The prevalence of a blood glucose concentration of < 47 mg/dl was 2.2% (31/1416): 95% CI 1.2%, 3.9%. The risk factors for neonatal hypoglycemia were delayed breastfeeding initiation [adjusted mean difference, - 2.6; 95% CI, - 4.4, - 0.79] and child age of 3 days or less [adjusted mean, - 12.2; 95% CI, - 14.0, - 10.4].
Conclusion: The incidence of neonatal hypoglycemia was low in this community and was predicted by delay in initiating breastfeeding and a child age of 3 days or less. We therefore suggest targeted screening and management of neonatal hypoglycemia among neonates before 3 days of age and those who are delayed in the onset of breastfeeding.

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Waterless Hand Cleansing with Chlorhexidine during the Neonatal Period by Mothers and Other Household Members: Findings from a Randomized Controlled Trial

Pavani K Ram[1], Farzana Begum[2], Christina Crabtree-Ide[1], Mohammad Rofi Uddin[2], Anne M Weaver[1], Md Golam Dostogir Harun[2], Jelena V Allen[2], Swapna Kumar[2], Sharifa Nasreen[1], Stephen P Luby[3 2], Shams El Arifeen[2]

Abstract

Observational data suggest maternal handwashing with soap prevents neonatal mortality. We tested the impact of a chlorhexidine-based waterless hand cleansing promotion on the behavior of mothers and other household members. In rural Bangladesh in 2014, we randomized consenting pregnant women to chlorhexidine provision and hand cleansing promotion or standard practices. We compared hand cleansing with chlorhexidine or handwashing with soap before baby care, among mothers and household members in the two groups, and measured chlorhexidine use in the intervention arm. Chlorhexidine was observed in the baby's sleep space in 97% of 130 intervention homes, versus soap in 59% of 128 control homes. Hand cleansing before baby care was observed 5.6 times more frequently among mothers in the intervention arm than in the controls (95% CI = 4.0-7.7). Hand cleansing was significantly more frequently observed in the intervention arm among women other than the mother (RR = 10.9) and girls (RR = 37.0). Men and boys in the intervention arm cleansed hands before 29% and 44% of baby care events, respectively, compared with 0% in the control arm. The median number of grams consumed during the neonatal period was 176 (IQR = 95-305 g), about 7.8 g/day (IQR = 4.2-13.8 g). Promotion of waterless chlorhexidine increased hand cleansing behavior among mothers and other household members. Discrepancy between observed use and measured chlorhexidine consumption suggested courtesy bias in structured observations. A waterless hand cleanser may represent one component of the multimodal strategies to prevent neonatal infections in low-resource settings.

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Can an mhealth clinical decision-making support system improve adherence to neonatal healthcare protocols in a low-resource setting?

Hannah Brown Amoakoh[1 2], Kerstin Klipstein-Grobusch[3 4], Irene Akua Agyepong[5], Mary Amoakoh-Coleman[6], Gbenga A Kayode[3 7], J B Reitsma[3], Diederick E Grobbee[3], Evelyn K Ansah[8]

Abstract

Background: This study assessed health workers' adherence to neonatal health protocols before and during the implementation of a mobile health (mHealth) clinical decision-making support system (mCDMSS) that sought to bridge access to neonatal health protocol gap in a low-resource setting.

Methods: We performed a cross-sectional document review within two purposively selected clusters (one poorly-resourced and one well-resourced), from each arm of a cluster-randomized trial at two different time points: before and during the trial. The total trial consisted of 16 clusters randomized into 8 intervention and 8 control clusters to assess the impact of an mCDMSS on neonatal mortality in Ghana. We evaluated health workers'

adherence (expressed as percentages) to birth asphyxia, neonatal jaundice and cord sepsis protocols by reviewing medical records of neonatal in-patients using a checklist. Differences in adherence to neonatal health protocols within and between the study arms were assessed using Wilcoxon rank-sum and permutation tests for each morbidity type. In addition, we tracked concurrent neonatal health improvement activities in the clusters during the 18-month intervention period.
Results: In the intervention arm, mean adherence was 35.2% (SD = 5.8%) and 43.6% (SD = 27.5%) for asphyxia; 25.0% (SD = 14.8%) and 39.3% (SD = 27.7%) for jaundice; 52.0% (SD = 11.0%) and 75.0% (SD = 21.2%) for cord sepsis protocols in the pre-intervention and intervention periods respectively. In the control arm, mean adherence was 52.9% (SD = 16.4%) and 74.5% (SD = 14.7%) for asphyxia; 45.1% (SD = 12.8%) and 64.6% (SD = 8.2%) for jaundice; 53.8% (SD = 16.0%) and 60.8% (SD = 11.7%) for cord sepsis protocols in the pre-intervention and intervention periods respectively. We observed nonsignificant improvement in protocol adherence in the intervention clusters but significant improvement in protocol adherence in the control clusters. There were 2 concurrent neonatal health improvement activities in the intervention clusters and over 12 in the control clusters during the intervention period.
Conclusion: Whether mHealth interventions can improve adherence to neonatal health protocols in low-resource settings cannot be ascertained by this study. Neonatal health improvement activities are however likely to improve protocol adherence. Future mHealth evaluations of protocol adherence must account for other concurrent interventions in study contexts.

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doi: 10.1186/s12913-021-06481-6.
Effectiveness of self-managed continuous monitoring for maintaining high-quality early essential newborn care compared to supervision visit in Lao PDR: a cluster randomised controlled trial
Sayaka Horiuchi[1], Sommana Rattana[2], Bounnack Saysanasongkham[3], Outhevanh Kounnavongsa[4], Shogo Kubota[4], Mariko Inoue[5], Kazue Yamaoka[5]
Abstract
Background: Thousands of neonatal deaths are expected to be averted by introducing the Early Essential Newborn Care (EENC) in the Western Pacific Region. In Lao People's Democratic Republic (Lao PDR), the government adopted the EENC programme and expanded it to district hospitals. With the expansion, maintaining the quality of EENC has become difficult for the government.
Methods: A cluster randomised controlled trial with four strata based on province and history of EENC coaching was implemented to evaluate the effectiveness of self-managed continuous monitoring compared with supervisory visit in Lao PDR between 20 July 2017 and 2 April 2019. Health workers who were routinely involved in maternity care were recruited from 15 district hospitals in Huaphanh (HP) and Xiangkhouang (XK) provinces. The primary endpoint was the score on the determinants of EENC performance measured by the Theory of Planned Behaviour (TPB). Secondary endpoints were set as the knowledge and skill scores. A linear mixed-effects model was applied to test the effects of intervention over time on the endpoints.

Results: Among 198 recruited health workers, 46 (23.2%) did not complete the final evaluation. TPB scores were 180.9 [Standard Deviation: SD 38.6] and 182.5 [SD 37.7] at baseline and 192.3 [SD 30.1] and 192.3 [SD 28.4] at the final evaluation in the intervention and control groups, respectively. There was no significant difference in changes between the groups in the adjusted model (2.4, p = 0.650). Interviews with participants revealed that district hospitals in HP regularly conducted peer reviews and feedback meetings, while few hospitals did in XK. Accordingly, in stratified analyses, the TPB score in the intervention group significantly increased in HP (15.5, p = 0.017) but largely declined in XK (- 17.7, p = 0.047) compared to the control group after adjusting for covariates. Skill scores declined sharper in the intervention group in XK (- 8.78, p = 0.026), particularly in the practice of managing nonbreathing babies.
Conclusions: The study indicates that self-managed continuous monitoring is effective in improving behaviour among district health workers; however, additional measures are necessary to support its proper implementation. To maintain resuscitation skills, repeated practice is necessary.
Trial registration: This trial was registered at UMIN Clinical Trials Registry on 15/6/2017. Registration number is UMIN000027794 .
Keywords: EENC; Neonatal care; Quality improvement; Resource-limited settings.

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Components of clean delivery kits and newborn mortality in the Zambia Chlorhexidine Application Trial (ZamCAT): An observational study
Jason H Park[1], Davidson H Hamer[2 3], Reuben Mbewe[4], Nancy A Scott[2], Julie M Herlihy[5], Kojo Yeboah-Antwi[6], Katherine E A Semrau[7 8 9 10]
Abstract
Background: Neonatal infection, a leading cause of neonatal death in low- and middle-income countries, is often caused by pathogens acquired during childbirth. Clean delivery kits (CDKs) have shown efficacy in reducing infection-related perinatal and neonatal mortality. However, there remain gaps in our current knowledge, including the effect of individual components, the timeline of protection, and the benefit of CDKs in home and facility deliveries.
Methods and findings: A post hoc secondary analysis was performed using nonrandomized data from the Zambia Chlorhexidine Application Trial (ZamCAT), a community-based, cluster-randomized controlled trial of chlorhexidine umbilical cord care in Southern Province of Zambia from February 2011 to January 2013. CDKs, containing soap, gloves, cord clamps, plastic sheet, razor blade, matches, and candle, were provided to all participants (pregnant women). Field monitors made a home-based visit to each participant 4 days postpartum, during which CDK use and newborn outcomes were ascertained. Logistic regression was used to study the association between different CDK components and neonatal mortality rate (NMR). Of 38,579 deliveries recorded during the study, 36,996 newborns were analyzed after excluding stillbirths and those with missing information. Gloves, cord clamps, and plastic sheets were the most frequently used CDK item combination in both home and facility deliveries. Each of the 7 CDK components was associated with lower NMR in users versus nonusers. Adjusted logistic regression showed that use of gloves (odds ratio [OR] 0.33,

95% CI 0.24-0.46), cord clamp (OR 0.51, 95% CI 0.38-0.68), plastic sheet (OR 0.46, 95% CI 0.34-0.63), and razor blade (OR 0.69, 95% CI 0.53-0.89) were associated with lower risk of newborn mortality. Use of gloves and cord clamp were associated with reduced risk of immediate newborn death (<24 hours). Reduction in risk of early newborn death (1-6 days) was associated with use of gloves, cord clamps, plastic sheets, and razor blades. In examining perinatal mortality (stillbirth plus neonatal death in the first 7 days of life), similar patterns were observed. There was no significant reduction in risk of late newborn mortality (7-28 days) with CDK use. Study limitations included potential recall bias of CDK use and inability to establish causality, as this was a secondary observational study.
Conclusions: CDK use was associated with reductions in early newborn mortality at both home and facility deliveries, especially when certain kit components were used. While causality could not be established in this nonrandomized secondary analysis, given these beneficial associations, scaling up the use of CDKs in rural areas of sub-Saharan Africa may improve neonatal outcomes.

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Effect of an integrated neonatal care kit on cause-specific neonatal mortality in rural Pakistan

Jessica Duby[1], Lisa G Pell[2], Shabina Ariff[3], Amira Khan[2], Afsah Bhutta[2], Daniel S Farrar[2], Diego G Bassani[2,4,5], Masawar Hussain[3], Zulfiqar A Bhutta[2,3,4], Sajid Soofi[3], Shaun K Morris[2,4,5]

Abstract
Background: In 2018, Pakistan had the world's highest neonatal mortality rate. Within Pakistan, most neonatal deaths occur in rural areas where access to health facilities is limited, and robust vital registration systems are lacking. To improve newborn survival, there is a need to better understand the causes of neonatal death in high burden settings and engage caregivers in the promotion of newborn health.
Objective: To describe the causes of neonatal death in a rural area in Pakistan and to estimate the effect of an integrated neonatal care kit (iNCK) on cause-specific neonatal mortality.
Methods: We analyzed data from a community-based, cluster-randomized controlled trial of 5286 neonates in Rahim Yar Khan (RYK), Punjab, Pakistan between April 2014 and August 2015. In intervention clusters, Lady Health Workers (LHW) delivered the iNCK and education on its use to pregnant women while control clusters received the local standard of care. The iNCK included interventions to prevent and identify signs of infection, identify low birthweight (LBW), and identify and manage hypothermia. Verbal autopsies were attempted for all deaths. The primary outcome was cause-specific neonatal mortality.
Results: Verbal autopsies were conducted for 84 (57%) of the 147 reported neonatal deaths. The leading causes of death were infection (44%), intrapartum-related complications (26%) and prematurity/LBW (20%). There were no significant differences in neonatal mortality due to prematurity/LBW (RR 0.43; 95% CI 0.15-1.24), infection (RR 1.10; 95% CI 0.58-2.10) or intrapartum-related complications (RR 1.04; 95% CI 0.0.45-2.41) among neonates who died in the intervention arm compared to those who died in the control arm.

Conclusion: The major causes of neonatal deaths in RYK, Pakistan mirror the global landscape of neonatal deaths. The iNCK did not significantly reduce any cause-specific neonatal mortality.

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EMBRACE intervention to improve the continuum of care in maternal and newborn health in Ghana: The RE-AIM framework-based evaluation

Kimiyo Kikuchi[1,2], Margaret Gyapong[3,4], Akira Shibanuma[1], Evelyn Asah[3,5], Sumiyo Okawa[1,6], Sheila Addei[4], Keiko Nanishi[7], Charlotte Tawiah[8], Junko Yasuoka[9], Francis Yeji[10], Abraham Oduro[10], Seth Owusu-Agyei[3,8], Gloria Quansah-Asare[11], Abraham Hodgson[5], Masamine Jimba[1], Ghana EMBRACE Implementation Research Team

Abstract

Background: Improving maternal and newborn health remains one of the most critical public health challenges, particularly in low- and lower-middle-income countries. To overcome this challenge, interventions to improve the continuum of care based on real-world settings need to be provided. The Ghana Ensure Mothers and Babies Regular Access to Care (EMBRACE) Implementation Research Team conducted a unique intervention program involving over 21 000 women to improve the continuum of care, thereby demonstrating an intervention program's effectiveness in a real-world setting. This study evaluates the implementation process of the EMBRACE intervention program based on the RE-AIM framework.

Methods: A cluster-randomized controlled trial was conducted in 32 sub-district-based clusters in Ghana. Interventions comprised of four components, and to evaluate the implementation process, we conducted baseline and endline questionnaire surveys for women who gave birth and lived in the study site. The key informant interviews of health workers and intervention monitoring were conducted at the health facilities in the intervention area. The data were analyzed using 34 components of the RE-AIM framework and classified under five general criteria (Reach, Effectiveness, Adoption, Implementation, and Maintenance).

Results: In total, 1480 and 1490 women participated in the baseline and endline questionnaire survey, respectively. In the intervention area, 83.8% of women participated (reach). The completion rate of the continuum of care increased from 7.5% to 47.1%. Newborns who had danger signs immediately after birth decreased after the intervention (relative risk = 0.82, 95% confidence interval = 0.68-0.99) (effectiveness). In the intervention area, 94% of all health facilities participated. Mothers willing to use their continuum of care cards in future pregnancies reached 87% (adoption). Supervision and manual use resolved the logistical and human resource challenges identified initially (implementation). The government included the continuum of care measures in their routine program and developed a new Maternal and Child Health Record Book, which was successfully disseminated nationwide (maintenance).

Conclusions: Following the RE-AIM framework evaluation, the EMBRACE intervention program was considered effective and as having great potential for scaling across in real-world settings, especially where the continuum of care needs to be improved.

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doi: 10.1542/peds.2020-015404.

Umbilical Cord Management at Term and Late Preterm Birth: A Meta-analysis

Judith Gomersall[1], Slavica Berber[2], Philippa Middleton[3], Susan J McDonald[4], Susan Niermeyer[5], Walid El-Naggar[6], Peter G Davis[7], Georg M Schmölzer[8], Colleen Ovelman[9], Roger F Soll[9], INTERNATIONAL LIAISON COMMITTEE ON RESUSCITATION NEONATAL LIFE SUPPORT TASK FORCE

Abstract

Context: The International Liaison Committee on Resuscitation prioritized scientific review of umbilical cord management at term and late preterm birth.

Objective: To assess effects of umbilical cord management strategies (clamping timing and cord milking) in infants ≥34 weeks' gestational age.

Data sources: Cochrane Central Register of Controlled Trials, Medline, PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, and trial registries searched July 2019.

Study selection: Two authors independently assessed eligibility of randomized controlled trials.

Data extraction: Two authors independently extracted data and assessed evidence certainty (Grading of Recommendations Assessment, Development and Evaluations).

Results: We identified 46 studies (9159 women and their infants) investigating 7 comparisons. Compared with early cord clamping (ECC) <30 seconds, delayed cord clamping (DCC) ≥30 seconds (33 studies), intact-cord milking (1 study), and cut-cord milking (2 studies) probably improve hematologic measures but may not affect survival without neurodisability, anemia in early infancy, or maternal postpartum hemorrhage. No differences in major neonatal morbidities are seen in studies comparing methods of optimizing placental transfusion (DCC versus cut-cord milking [3 studies], longer delays in clamping [7 studies], or physiologic parameters [3 studies]). Strategies that promote increased placental transfusion may be associated with greater phototherapy use. Evidence for all outcomes was low or very low certainty.

Limitations: Incompleteness and low certainty of findings limit applicability.

Conclusions: Compared with ECC, DCC or cord milking increases hemoglobin and hematocrit immediately after birth in infants ≥34 weeks' gestational age. The uncertain effects of DCC and cord milking compared with ECC on major morbidities limit usefulness of available evidence for policy and practice.

Eur J Pediatr. 2021 Jun;180(6):1701-1710.
doi: 10.1007/s00431-021-03959-7. Epub 2021 Jan 21.

Effects of delayed cord clamping in intrauterine growth-restricted neonates: a randomized controlled trial

Kanhu Charan Digal[1], Poonam Singh[1], Yash Srivastava[2], Jaya Chaturvedi[3], Amit Kumar Tyagi[4], Sriparna Basu[5]

Abstract

The time of cord clamping in intrauterine growth-restricted (IUGR) neonates remains an area of uncertainty. This assessor-blinded randomized controlled trial compared the effects of delayed cord clamping (DCC) with early cord clamping (ECC) on the systemic blood flow (SBF) and cerebral hemodynamics in IUGR neonates of gestational age ≥28 weeks, not requiring resuscitation. Eligible newborns were randomized to DCC (cord clamping after 60 s; n=55) or ECC (cord clamping within 30 s; n=55) group immediately after delivery. The primary outcome variable was superior vena cava (SVC) blood flow at 24±2 h. The secondary outcome variables were right ventricular output (RVO), anterior cerebral artery (ACA) blood flow velocity (BFV), superior mesenteric artery (SMA)-BFV and venous hematocrit at 24±2 h, peak total serum bilirubin (TSB), incidences of polycythemia, intraventricular hemorrhage, respiratory distress, feeding intolerance, and necrotizing enterocolitis, outcome, duration of hospital stay, screening audiometry, and serum ferritin levels at the postnatal age of 3 months. Compared to ECC, DCC was associated with significantly higher SVC flow (101.22±21.02 and 81.27±19.12 mL/kg/min, in DCC and ECC groups, respectively; p<0.0001), and significantly increased RVO, SMA-BFV, venous hematocrit, and serum ferritin levels. Though peak TSB was significantly higher with DCC, duration of phototherapy was comparable. ACA-BFV, incidence of polycythemia, and other outcomes were comparable between the groups.Conclusions: DCC was a safe and beneficial intervention in IUGR infants with an improved SBF and SMA-BFV and an increased hematocrit and serum ferritin levels without higher incidences of polycythemia and requirement of phototherapy for significant hyperbilirubinemia.

Delayed cord clamping (DCC) increases superior vena cava (SVC) blood flow in preterm neonates. • DCC increases hematocrit and serum ferritin in intrauterine growth-restricted (IUGR) neonates, but there may be an associated risk of polycythemia and neonatal hyperbilirubinemia. What is New: • DCC increases SVC blood flow, right ventricular output, superior mesenteric artery blood flow velocity, venous hematocrit, and serum ferritin in IUGR neonates. • Incidences of polycythemia and duration of phototherapy for significant neonatal hyperbilirubinemia do not increase with DCC.

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Epub 2020 Sep 16.

Effect of Umbilical Cord Milking vs Delayed Cord Clamping on Venous Hematocrit at 48 Hours in Late Preterm and Term Neonates: A Randomized Controlled Trial

Mukul Kumar Mangla[1], Anu Thukral[2], M Jeeva Sankar[1], Ramesh Agarwal[1], Ashok K Deorari[1], V K Paul[1]

Abstract

Objective: To compare the effect of intact umbilical cord milking (MUC) and delayed cord clamping (DCC) on venous hematocrit at 48 (±6) hours in late preterm and term neonates (350/7- 426/7 wk).

Study design: Randomized trial.

Setting and participants: All late preterm and term neonates (350/7 - 426/7 wk) neonates born in the labor room and maternity operation theatre of tertiary care unit were included.

Intervention: We randomly allocated enrolled neonates to MUC group (cord milked four times towards the baby while being attached to the placenta; n=72) or DCC group (cord clamped after 60 seconds; n=72).
Outcome: Primary outcome was venous hematocrit at 48 (±6) hours of life. Additional outcomes were venous hematocrit at 48 (±6) hours in newborns delivered through lower segment caesarean section (LSCS), incidence of polycythemia requiring partial exchange transfusion, incidence of hyperbilirubinemia requiring phototherapy, and venous hematocrit and serum ferritin levels at 6 (±1) weeks of age.
Results: The mean (SD) hematocrit at 48 (±6) hours in the MUC group was higher than in DCC group [57.7 (4.3) vs. 55.9 (4.4); P=0.002]. Venous hematocrit at 6 (±1) weeks was higher in MUC than in DCC group [mean (SD), 37.7 (4.3) vs. 36 (3.4); mean difference 1.75 (95% CI 0.53 to 2.9); P=0.005]. Other parameters were similar in the two groups.
Conclusion: MUC leads to a higher venous hematocrit at 48 (±6) hours in late preterm and term neonates when compared with DCC.

J Matern Fetal Neonatal Med. 2021 Feb 10;1-11.
doi: 10.1080/14767058.2021.1884676. Online ahead of print.
Umbilical cord milking versus delayed cord clamping in term and late-preterm infants: a systematic review and meta-analysis
Amrit Jeevan[1], Anitha Ananthan[2], Manjari Bhuwan[1], Haribalakrishna Balasubramanian[3], Shripada Rao[4], Nandkishor S Kabra[3]
Abstract
Objective: To conduct a systematic review and meta-analysis to compare the efficacy and safety of umbilical cord milking (UCM) versus delayed cord clamping (DCC) in term and late-preterm infants.
Methods: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Clinical trial registries, and Gray literature were searched for randomized controlled trials (RCTs) comparing UCM with DCC in term and late-preterm infants for both short-term and long-term outcomes. Intact and cut UCM were compared separately with DCC using subgroup analysis. We used fixed effect model to pool the data. Random effects model was used when there was significant heterogeneity.
Results: Nine studies (1632 infants) were included in the systematic review. Milking was performed on intact cord (i-UCM) in five studies (*n* = 829) and on cut cord (c-UCM) in four studies (*n* = 803). Cord milking significantly improved hemoglobin level at 48-72 h of life when compared to DCC (six studies, *n* = 924, mean difference 0.36 g/dL; 95% CI: 0.19-0.53). In addition, hemoglobin level at six to eight weeks of age was also significantly higher in the studies comparing i-UCM with DCC (two studies, *n* = 550: mean difference 0.16 g/dL; 95% CI: 0.06-0.27). There was no difference between the UCM group and DCC group for any other outcome. Only one study provided information on growth and hematological parameters at one year of age. Neurodevelopmental outcomes were not reported. None of the studies included non-vigorous infants. The grade of evidence was low to very low for all the outcomes studied.
Conclusion: UCM is comparable to DCC in improving short-term hematological outcomes in term and late-preterm vigorous infants. Trials assessing the effect of UCM on important

clinical and long-term outcomes among non-vigorous mature preterm infants are urgently required.

BMC Pregnancy Childbirth. 2020 Sep 16;20(1):540.
doi: 10.1186/s12884-020-03239-6.

Coverage of the WHO's four essential elements of newborn care and their association with neonatal survival in southern Nepal

Emily Bryce[1], Luke C Mullany[2], Subarna K Khatry[2 3], James M Tielsch[4], Steven C LeClerq[2 3], Joanne Katz[2]

Abstract

Background: Despite recent improvements in child survival, neonatal mortality continues to decline at a slower rate and now represents 47% of under-five deaths globally. The World Health Organization developed core indicators to better monitor the quality of maternal and newborn health services. One such indicator for newborn health is "the proportion of newborns who received all four elements of essential care". The four elements are immediate and thorough drying, skin to skin contact, delayed cord clamping, and early initiation of breastfeeding. Although there is existing evidence demonstrating an association with decreased neonatal mortality for each element individually, the cumulative impact has not yet been examined.

Methods: This analysis uses data from a randomized trial to examine the impact of sunflower versus mustard seed oil massage on neonatal mortality and morbidity in the Sarlahi district in Southern Nepal from 2010 to 2017. The proportion of newborn infants receiving an intervention was the exposure and neonatal mortality was the outcome in this analysis. Neonatal mortality was defined as a death between three hours and less than 28 days of age. Associations between neonatal mortality and the essential elements were estimated by Cox proportion hazards models. The hazard ratios and corresponding 95% confidence intervals were reported.

Results: 28,121 mother-infant pairs and 753 neonatal deaths were included. The percent receiving the individual elements ranged from 19.5% (skin to skin contact) to 68.2% (delayed cord clamping). The majority of infants received one or two of the elements of essential care, with less than 1% receiving all four. Skin to skin contact and early initiation of breastfeeding were associated with lower risk of neonatal mortality (aHR = 0.64 [0.51, 0.81] and aHR = 0.72 [0.60, 0.87], respectively). The risk of mortality declined as the number of elements received increased; receipt of one element compared to zero was associated with a nearly 50% reduction in risk of mortality and receipt of all four elements resulted in a 72% decrease in risk of mortality.

Conclusions: The receipt of one or more of the four essential elements of newborn care was associated with improved neonatal survival. The more elements of care received, the more survival improved.

BMC Res Notes. 2020 Sep 14;13(1):430.
doi: 10.1186/s13104-020-05282-0.

Newborn's first bath: any preferred timing? A pilot study from Lebanon

Joelle Mardini[1,2], Clara Rahme[3], Odette Matar[4], Sophia Abou Khalil[4], Souheil Hallit[5,6], Marie-Claude Fadous Khalife[7,8]

Abstract

Objective: To try to find the most appropriate time for the newborn's first bath. This prospective randomized study was conducted in one hospital (July-September 2017).

Results: A higher percentage of newborns who had a skin-to-skin contact with their mothers had their bath at 24 h vs 2 h after birth (65.2% vs 33.3%; p = 0.01). A higher percentage of mothers who helped in their baby's bath had their baby's bath at 24 h vs 2 h (65.2% vs 5.9%; p < 0.001) and vs 6 h (65.2% vs 15.7%; p < 0.001) respectively. A higher mean incubation time was seen between newborns who had their bath at 2 h (2.10 vs 1.78; p = 0.002) and 6 h (2.18 vs 1.78; p = 0.003) compared to those who had their bath at 24 h respectively. A higher percentage of newborns who took their first bath 24 h after birth were calm compared to crying vigorously (38.6% vs 9.1%; p = 0.04). Delaying newborn first bath until 24 h of life was associated with benefits (reducing hypothermia and vigorous crying, benefit from the vernix caseosa on the skin and adequate time of skin-to-skin contact and mother participation in her child's bathing.

Neonatal respiratory and intensive care

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doi: 10.1055/s-0041-1726122. Online ahead of print.

Efficacy and Safety of Two Different Flow Rates of Nasal High-Flow Therapy in Preterm Neonates ≥28 Weeks of Gestation: A Randomized Controlled Trial

Haribalakrishna Balasubramanian[1], Sachin Sakharkar[1], Swati Majarikar[1], Lakshmi Srinivasan[2], Nandkishor S Kabra[1], Bhawandeep Garg[1], Javed Ahmed[1]

Abstract

Objective: The study aimed to compare the efficacy and safety of two different nasal high-flow rates for primary respiratory support in preterm neonates STUDY DESIGN: In this single-center, double-blinded randomized controlled trial, preterm neonates ≥28 weeks of gestation with respiratory distress from birth were randomized to treatment with either increased nasal flow therapy (8-10 L/min) or standard nasal flow therapy (5-7 L/min). The primary outcome of nasal high-flow therapy failure was a composite outcome defined as the need for higher respiratory support (continuous positive airway pressure [CPAP] or mechanical ventilation) or surfactant therapy.

Results: A total of 212 neonates were enrolled. Nasal high-flow failure rate in the increased flow group was similar to the standard flow group (22 vs. 29%, relative risk = 0.81 [95% confidence interval: 0.57-1.15]). However, nasal flow rate escalation was significantly more common in the standard flow group (64 vs. 43%, *p* = 0.004). None of the infants in the increased flow group developed air leak syndromes.

Conclusion: Higher nasal flow rate (8-10 L/min) when compared with lower nasal flow rate of 5 to 7 L/min did not reduce the need for higher respiratory support (CPAP/mechanical ventilation) or surfactant therapy in moderately and late preterm neonates. However, initial

flow rates of 5 L/min were not optimal for most preterm infants receiving primary nasal flow therapy.

J Trop Pediatr. 2021 Jan 29;67(1):fmaa097.
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Sustained Lung Inflation in Pre-term Infants at Birth: A Randomized Controlled Trial

Walaa A Abuel Hamd[1], Douaa E El Sherbiny[1], Salma Z El Houchi[1], Iman F Iskandar[1], Dina M Akmal[1]

Abstract

Background: Invasive mechanical ventilation (IMV) of pre-term infants may be associated with high rate of mortality and iatrogenic complications in low- and middle-income countries. Sustained lung inflation (SLI) may help to reduce their need for IMV.

Methods: This randomized controlled trial included 160 infants with gestational age (GA) ≥27 and ≤32 weeks who were randomly assigned to receive either SLI; using a pressure of 20 cmH2O for 15 s followed by nasal continuous positive airway pressure (CPAP) of 5 cmH2O or nasal CPAP alone, through an appropriate mask and a T-piece resuscitator. Primary outcome was the need for IMV in the first 72 h of life.

Results: There was no difference in the primary outcome between SLI group; 55% (44 out of 80) and the control group; 65% (52 out of 80) [odds ratio (OR): 0.623, 95% confidence interval (CI): 0.33-1.18; p = 0.145]. However, SLI significantly reduced the primary outcome in the sicker infants; who had clinical eligibility criteria (CEC; OR: 0.224, 95% CI: 0.076-0.663; p = 0.005) and in the smaller babies; whose GA was <30 weeks (OR: 0.183, 95% CI: 0.053-0.635; p = 0.005).

Conclusion: SLI was not harmful. Although, it did not lead to reduction in the need for IMV in the first 72 h of life in pre-term infants with GA ≥27 and ≤32 weeks, SLI reduced this outcome in the subgroup of infants with CEC and those with GA <30 weeks. Future trials are needed to investigate the effect of SLI on these two subgroups.

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Heated Humidified High-Flow Nasal Cannula vs. Nasal Continuous Positive Airway Pressure for Post-extubation Respiratory Support in Preterm Infants: A Randomized Controlled Trial

Rameshwor Yengkhom[1], Pradeep Suryawanshi[2], Bhvya Gupta[2], Sujata Deshpande[2]

Abstract

Objective: The objective of this study was to compare the efficacy and safety of heated humidified high-flow nasal cannula (HHHFNC) and nasal continuous positive airway pressure (nCPAP) for prevention of extubation failure in preterm infants.

Methods: Preterm infants (gestation ≥28 weeks) were randomized to HHHFNC or nCPAP after extubation. Primary outcome was extubation failure within 72 h of extubation.

Results: A total of 128 preterm infants were randomized to receive either HHHFNC (n = 63) or nCPAP (n = 65) after extubation. The primary outcome of extubation failure within 72 h after extubation was not different between the two groups (HHHFNC, 22.2% vs. nCPAP, 18.5%, risk

difference of 3.7% and 95% CI -10.3 to 17.6, p = 0.604). The incidence of nasal trauma was significantly lower in the HHHFNC group than in the nCPAP group 6.3% vs. 21.5%, p = 0.020. **Conclusions:** In our study, HHHFNC was as effective as nCPAP for prevention of extubation failure in preterm infants. Also, HHHFNC was associated with significantly less nasal trauma compared with nCPAP.

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Nasal HFOV versus nasal IPPV as a post-extubation respiratory support in preterm infants-a randomised controlled trial

Soutrik Seth[1], Bijan Saha[2], Anindya Kumar Saha[1], Suchandra Mukherjee[1], Avijit Hazra[3]

Abstract

Early and successful extubation prevents several morbidities in preterm newborns. Several secondary non-invasive respiratory modalities exist but with their merits and demerits. Given the benefits of nasal high-frequency oscillatory ventilation (nHFOV), we tried to examine whether nHFOV could reduce reintubation rates compared to nasal intermittent positive pressure ventilation (NIPPV) during the post-extubation phase in preterm infants. Stratified randomisation based on gestational age was done for 86 mechanically ventilated preterm infants between 26 and 36^{+6} weeks of gestation within 2 weeks of age to receive either nHFOV or NIPPV post-extubation. The main objective was to compare extubation failure within 72 h following extubation and secondarily feed intolerance, intraventricular haemorrhage (IVH) (> grade 3), composite bronchopulmonary dysplasia (BPD)/mortality, composite duration of oxygen supplementation/ventilation support and SpO2/FiO2 ratio. No statistical difference was noted for primary outcome (RR 0.8, 95% CI: 0.23 to 2.78; p = 1.00) and secondary outcomes. However, nHFOV appeared possibly better in respect to feed tolerance rates and pCO2 washout.Conclusion: Extubation failure within 72 h in infants less than 37 weeks of gestation did not differ between the two groups. However, nHFOV seems promising in reducing enteral feeding issues and pCO2 elimination. Larger multicentre studies are required for exploring benefits of nHFOV.

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Gastric Lavage for Prevention of Feeding Intolerance in Neonates Delivered Through Meconium-Stained Amniotic Fluid: A Systematic Review and Meta-Analysis

Poonam Singh[1], Manish Kumar[2], Sriparna Basu[3]

Abstract

Background: The role of gastric lavage in neonates delivered through meconium-stained amniotic fluid remains unclear.

Objectives: This study evaluated the effects of gastric lavage, compared to no- gastric lavage, on the incidences of feeding intolerance, respiratory distress, meconium aspiration syndrome, time to establish breastfeeding, hospitalization and procedure-related complications in late-preterm and term neonates delivered through meconium-stained amniotic fluid.

Design: Systematic review and meta-analysis.

Data sources and selection criteria: MEDLINE, EMBASE, CENTRAL, and other databases were searched for randomized controlled trials and quasi randomized controlled trials using search terms: neonate OR newborn infant, meconium OR meconium-stained amniotic fluid, and lavage OR gastric lavage from inception to May 2020. Data were pooled in RevMan and analyzed in GRADE.
Results: Pooled effects (9 randomized controlled trials, number=3668), showed a significant reduction in the incidence of feeding intolerance (relative risk 0.70; 95% confidence interval 0.58,0.85, I2=0) after gastric lavage. No difference was observed for the incidence of meconium aspiration syndrome (4 studies) or procedure-related complications (7 studies). Only one study reporting the proportion of neonates with low oxygenation (SpO2<85%), did not find any significant difference. No study evaluated the effects of gastric lavage on respiratory distress, breastfeeding, and hospitalization.
Conclusions: Low-quality evidence supported the role of gastric lavage for the prevention of feeding intolerance in late-preterm and term neonates born through meconium-stained amniotic fluid. Applicability of results was limited by the high risk-of-bias. Well-conducted randomized controlled trials with important patient outcomes are needed before recommending the practice of gastric lavage.

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Fluid restriction in the management of transient tachypnea of the newborn

Neeraj Gupta[1], Matteo Bruschettini[2], Deepak Chawla[3]

Abstract
Background: Transient tachypnea of the newborn (TTN) is caused by delayed clearance of lung fluid at birth. TTN typically appears within the first two hours of life in term and late preterm neonates and is characterized by tachypnea and signs of respiratory distress. Although it is usually a self-limited condition, admission to a neonatal unit is frequently required for monitoring and providing respiratory support. Restricting intake of fluids administered to these infants in the first days of life might improve clearance of lung liquid, thus reducing the effort required to breathe, improving respiratory distress, and potentially reducing the duration of tachypnea.
Objectives: To evaluate the efficacy and safety of restricted fluid therapy as compared to standard fluid therapy in decreasing the duration of oxygen administration and the need for noninvasive or invasive ventilation among neonates with TTN.
Search methods: We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 12), in the Cochrane Library; Ovid MEDLINE and electronic ahead of print publications, in-process & other non-indexed citations, Daily and Versions(R); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), on December 6, 2019. We also searched clinical trial databases and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.
Selection criteria: We included randomized controlled trials (RCTs), quasi-RCTs, and cluster trials on fluid restriction in term and preterm neonates with the diagnosis of TTN or delayed adaptation during the first week after birth.
Data collection and analysis: For each of the included trials, two review authors independently extracted data (e.g. number of participants, birth weight, gestational age,

duration of oxygen therapy, need for continuous positive airway pressure [CPAP], need for mechanical ventilation, duration of mechanical ventilation) and assessed the risk of bias (e.g. adequacy of randomization, blinding, completeness of follow-up). The primary outcome considered in this review was the duration of supplemental oxygen therapy in hours or days. We used the GRADE approach to assess the certainty of evidence.
Main results: Four trials enrolling 317 infants met the inclusion criteria. Three trials enrolled late preterm and term infants with TTN, and the fourth trial enrolled only term infants with TTN. Infants were on various methods of respiratory support at the time of enrollment including room air, oxygen, or nasal CPAP. Infants in the fluid-restricted group received 15 to 20 mL/kg/d less fluid than those in the control group for varying durations after enrollment. Two studies had high risk of selection bias, and three out of four had high risk of performance bias. Only one study had low risk of detection bias, with two at high risk and one at unclear risk. The certainty of evidence for all outcomes was very low due to imprecision of estimates and unclear risk of bias. Two trials reported the primary duration of supplemental oxygen therapy. We are uncertain whether fluid restriction decreases or increases the duration of supplemental oxygen therapy (mean difference [MD] -12.95 hours, 95% confidence interval [CI] -32.82 to 6.92; I^2 = 98%; 172 infants). Similarly, there is uncertainty for various secondary outcomes including incidence of hypernatremia (serum sodium > 145 mEq/L, risk ratio [RR] 4.0, 95% CI 0.46 to 34.54; test of heterogeneity not applicable; 1 trial, 100 infants), hypoglycemia (blood glucose < 40 mg/dL, RR 1.0, 95% CI 0.15 to 6.82; test of heterogeneity not applicable; 2 trials, 164 infants), endotracheal ventilation (RR 0.73, 95% CI 0.24 to 2.23; I^2 = 0%; 3 trials, 242 infants), need for noninvasive ventilation (RR 0.40, 95% CI 0.14 to 1.17; test of heterogeneity not applicable; 2 trials, 150 infants), length of hospital stay (MD -0.92 days, 95% CI -1.53 to -0.31; test of heterogeneity not applicable; 1 trial, 80 infants), and cumulative weight loss at 72 hours of age (%) (MD 0.24, 95% CI -1.60 to 2.08; I^2 = 89%; 2 trials, 156 infants). We did not identify any ongoing trials; however, one trial is awaiting classification.
Authors' conclusions: We found limited evidence to establish the benefits and harms of fluid restriction in the management of TTN. Given the very low certainty of available evidence, it is impossible to determine whether fluid restriction is safe or effective for management of TTN. However, given the simplicity of the intervention, a well-designed trial is justified.

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Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants
Jacqueline J Ho[1], Prema Subramaniam[2], Peter G Davis[3 4 5]
Abstract
Background: Respiratory distress, particularly respiratory distress syndrome (RDS), is the single most important cause of morbidity and mortality in preterm infants. In infants with progressive respiratory insufficiency, intermittent positive pressure ventilation (IPPV) with surfactant has been the usual treatment, but it is invasive, potentially resulting in airway and lung injury. Continuous positive airway pressure (CPAP) has been used for the prevention and treatment of respiratory distress, as well as for the prevention of apnoea, and in weaning from IPPV. Its use in the treatment of RDS might reduce the need for IPPV and its sequelae.

Objectives: To determine the effect of continuous distending pressure in the form of CPAP on the need for IPPV and associated morbidity in spontaneously breathing preterm infants with respiratory distress.
Search methods: We used the standard strategy of Cochrane Neonatal to search CENTRAL (2020, Issue 6); Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions; and CINAHL on 30 June 2020. We also searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.
Selection criteria: All randomised or quasi-randomised trials of preterm infants with respiratory distress were eligible. Interventions were CPAP by mask, nasal prong, nasopharyngeal tube or endotracheal tube, compared with spontaneous breathing with supplemental oxygen as necessary.
Data collection and analysis: We used standard methods of Cochrane and its Neonatal Review Group, including independent assessment of risk of bias and extraction of data by two review authors. We used the GRADE approach to assess the certainty of evidence. Subgroup analyses were planned on the basis of birth weight (greater than or less than 1000 g or 1500 g), gestational age (groups divided at about 28 weeks and 32 weeks), timing of application (early versus late in the course of respiratory distress), pressure applied (high versus low) and trial setting (tertiary compared with non-tertiary hospitals; high income compared with low income) MAIN RESULTS: We included five studies involving 322 infants; two studies used face mask CPAP, two studies used nasal CPAP and one study used endotracheal CPAP and continuing negative pressure for a small number of less ill babies. For this update, we included one new trial. CPAP was associated with lower risk of treatment failure (death or use of assisted ventilation) (typical risk ratio (RR) 0.64, 95% confidence interval (CI) 0.50 to 0.82; typical risk difference (RD) -0.19, 95% CI -0.28 to -0.09; number needed to treat for an additional beneficial outcome (NNTB) 6, 95% CI 4 to 11; I^2 = 50%; 5 studies, 322 infants; very low-certainty evidence), lower use of ventilatory assistance (typical RR 0.72, 95% CI 0.54 to 0.96; typical RD -0.13, 95% CI -0.25 to -0.02; NNTB 8, 95% CI 4 to 50; I^2 = 55%; very low-certainty evidence) and lower overall mortality (typical RR 0.53, 95% CI 0.34 to 0.83; typical RD -0.11, 95% CI -0.18 to -0.04; NNTB 9, 95% CI 2 to 13; I^2 = 0%; 5 studies, 322 infants; moderate-certainty evidence). CPAP was associated with increased risk of pneumothorax (typical RR 2.48, 95% CI 1.16 to 5.30; typical RD 0.09, 95% CI 0.02 to 0.16; number needed to treat for an additional harmful outcome (NNTH) 11, 95% CI 7 to 50; I^2 = 0%; 4 studies, 274 infants; low-certainty evidence). There was no evidence of a difference in bronchopulmonary dysplasia, defined as oxygen dependency at 28 days (RR 1.04, 95% CI 0.35 to 3.13; I^2 = 0%; 2 studies, 209 infants; very low-certainty evidence). The trials did not report use of surfactant, intraventricular haemorrhage, retinopathy of prematurity, necrotising enterocolitis and neurodevelopment outcomes in childhood.
Authors' conclusions: In preterm infants with respiratory distress, the application of CPAP is associated with reduced respiratory failure, use of mechanical ventilation and mortality and an increased rate of pneumothorax compared to spontaneous breathing with supplemental oxygen as necessary. Three out of five of these trials were conducted in the 1970s. Therefore, the applicability of these results to current practice is unclear. Further studies in resource-poor settings should be considered and research to determine the most appropriate pressure level needs to be considered.

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doi: 10.1007/s40272-020-00412-4.

Efficacy of Milrinone Plus Sildenafil in the Treatment of Neonates with Persistent Pulmonary Hypertension in Resource-Limited Settings: Results of a Randomized, Double-Blind Trial

Mamdouh El-Ghandour[1], Bahaa Hammad[1], Mohamed Ghanem[1], Manal A M Antonios[2]

Abstract

Background: The management of severe persistent pulmonary hypertension (PPHN) can be very challenging in many resource-limited centers without access to inhaled nitric oxide or extracorporeal membrane oxygenation.

Objectives: The current study aimed to investigate the efficacy of oral sildenafil and intravenous milrinone infusion and compare the effects of these drugs in combination versus as monotherapy in neonates with PPHN.

Methods: A double-blind randomized controlled trial was conducted in which neonates with PPHN were divided into three groups of 20 patients each: group 1 received oral sildenafil starting at 0.5 mg/kg every 6 h to a target maintenance dose of 2 mg/kg every 6 h; group 2 received intravenous milrinone 0.5 µg/kg/min as a continuous infusion; and group 3 received both oral sildenafil and intravenous milrinone.

Results: Post-treatment pulmonary artery systolic pressure was significantly lower in group 3 than in groups 1 and 2, which both received monotherapy (p = 0.031). The oxygenation index also decreased significantly in the dual-therapy group (p = 0.002) compared with the monotherapy groups. Combined use of both drugs demonstrated a beneficial synergistic effect with better outcomes and reduced mortality.

Conclusion: Dual therapy using sildenafil and milrinone was superior to monotherapy with either drug in neonates with severe PPHN and is recommended for use in resource-constrained settings.

Low birth weight and prematurity

Kangaroo mother care and thermoregulation

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Immediate "Kangaroo Mother Care" and Survival of Infants with Low Birth Weight

WHO Immediate KMC Study Group; Sugandha Arya[1], Helga Naburi[1], Kondwani Kawaza[1], Sam Newton[1], Chineme H Anyabolu[1], Nils Bergman[1], Suman P N Rao[1], Pratima Mittal[1], Evelyne Assenga[1], Luis Gadama[1], Roderick Larsen-Reindorf[1], Oluwafemi Kuti[1], Agnes Linnér[1], Sachiyo Yoshida[1], Nidhi Chopra[1], Matilda Ngarina[1], Ausbert T Msusa[1], Adwoa Boakye-Yiadom[1], Bankole P Kuti[1], Barak Morgan[1], Nicole Minckas[1], Jyotsna Suri[1], Robert Moshiro[1], Vincent Samuel[1], Naana Wireko-Brobby[1], Siren Rettedal[1], Harsh V Jaiswal[1], M Jeeva Sankar[1], Isaac Nyanor[1], Hiresh Tiwary[1], Pratima Anand[1], Alexander A Manu[1], Kashika Nagpal[1], Daniel Ansong[1], Isha Saini[1], Kailash C Aggarwal[1], Nitya Wadhwa[1], Rajiv Bahl[1], Bjorn

Westrup[1], Ebunoluwa A Adejuyigbe[1], Gyikua Plange-Rhule[1], Queen Dube[1], Harish Chellani[1], Augustine Massawe[1]

Abstract

Background: "Kangaroo mother care," a type of newborn care involving skin-to-skin contact with the mother or other caregiver, reduces mortality in infants with low birth weight (<2.0 kg) when initiated after stabilization, but the majority of deaths occur before stabilization. The safety and efficacy of kangaroo mother care initiated soon after birth among infants with low birth weight are uncertain.

Methods: We conducted a randomized, controlled trial in five hospitals in Ghana, India, Malawi, Nigeria, and Tanzania involving infants with a birth weight between 1.0 and 1.799 kg who were assigned to receive immediate kangaroo mother care (intervention) or conventional care in an incubator or a radiant warmer until their condition stabilized and kangaroo mother care thereafter (control). The primary outcomes were death in the neonatal period (the first 28 days of life) and in the first 72 hours of life.

Results: A total of 3211 infants and their mothers were randomly assigned to the intervention group (1609 infants with their mothers) or the control group (1602 infants with their mothers). The median daily duration of skin-to-skin contact in the neonatal intensive care unit was 16.9 hours (interquartile range, 13.0 to 19.7) in the intervention group and 1.5 hours (interquartile range, 0.3 to 3.3) in the control group. Neonatal death occurred in the first 28 days in 191 infants in the intervention group (12.0%) and in 249 infants in the control group (15.7%) (relative risk of death, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P = 0.001); neonatal death in the first 72 hours of life occurred in 74 infants in the intervention group (4.6%) and in 92 infants in the control group (5.8%) (relative risk of death, 0.77; 95% CI, 0.58 to 1.04; P = 0.09). The trial was stopped early on the recommendation of the data and safety monitoring board owing to the finding of reduced mortality among infants receiving immediate kangaroo mother care.

Conclusions: Among infants with a birth weight between 1.0 and 1.799 kg, those who received immediate kangaroo mother care had lower mortality at 28 days than those who received conventional care with kangaroo mother care initiated after stabilization; the between-group difference favoring immediate kangaroo mother care at 72 hours was not significant.

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Disposable low-cost cardboard incubator for thermoregulation of stable preterm infant - a randomized controlled non-inferiority trial

Ashok Chandrasekaran[1], Prakash Amboiram[1], Umamaheswari Balakrishnan[1], Thangaraj Abiramalatha[1], Govind Rao[2], Shaik Mohammad Shafi Jan[1], Usha Devi Rajendran[1], Uma Sekar[3], Gayathri Thiruvengadam[4], Binu Ninan[1]

Abstract

Background: Incubators and radiant warmers are essential equipment in neonatal care, but the typical 1,500 to 35,000 USD cost per device makes it unaffordable for many units in low and middle-income countries. We aimed to determine whether stable preterm infants could maintain thermoregulation for 48 h in a low-cost incubator (LCI).

Methods: The LCI was constructed using a servo-heater costing 200 USD and cardboard infant-chamber. We conducted this open-labeled non-inferiority randomized controlled trial in a tertiary level teaching hospital in India from May 2017 to March 2018. Preterm infants on full feeds and receiving incubator or radiant warmer care were enrolled at 32 to 36 weeks post-menstrual age. We enrolled 96 infants in two strata (Strata-1< 33 weeks, Strata-2 ≥ 33 weeks at birth). Infants were randomized to LCI or standard single-wall incubator (SSI) after negative incubator cultures and monitored for 48 h in air-mode along with kangaroo mother care. The incubator temperature was adjusted manually to maintain skin and axillary temperatures between 36.5 °C and 37.5 °C. During post-infant period after 48 h, SSI and LCI worked for 5 days and incubator temperatures were measured. The primary outcome was maintenance of skin and axillary temperatures with a non-inferiority margin of 0.2 °C. Failed thermoregulation was defined as abnormal axillary temperature (< 36.5 °C or >37.5 °C) for > 30 continuous-minutes. Secondary outcomes were incidence of hypothermia and required incubator temperature. Trial registration details: Clinical Trial Registry - India (CTRI/2015/10/006316).
Findings: Prior to enrollment 79(82%) infants were in radiant warmer and 17(18%) infants were in incubator care. Median weight at enrollment in Strata-1 and Strata-2 for SSI vs. LCI was 1355(IQR 1250-1468) vs. 1415(IQR 1280-1582) and 1993(IQR 1595-2160) vs. 1995(IQR 1632-2237) grams. Mean skin temperature in Strata-1 and Strata-2 for SSI vs. LCI was 36.8 °*C* ± 0.2 vs. 36.7 °*C* ± 0.18 and 36.8 °*C* ± 0.22 vs. 36.7 °*C* ± 0.19. Mean axillary temperature in Strata-1 and Strata-2 for SSI vs. LCI was 36.9 °*C* ± 0.19 vs. 36.8 °*C* ± 0.16 and 36.8 °*C* ± 0.2 vs. 36.8 °*C* ± 0.19. Mixed-effect model done for repeated measures of skin and axillary temperatures showed the estimates were within the non-inferiority limit; -0.07 °C (95% CI -0.11 to -0.04) and -0.06 °C (95% CI -0.095 to -0.02), respectively. Failed thermoregulation did not occur in any infants. Mild hypothermia occurred in 11 of 48(23%) of SSI and 16 of 48(33%) of LCI, OR 1.28 (95%CI 0.85 to 1.91). Incubator temperature in LCI was higher by 0.7 °C (95%CI 0.52 to 0.91). In the post-infant period SSI and LCI had excellent reliability to maintain set-temperature with intra-class correlation coefficient of 0.93 (95%CI 0.92 to 0.94) and 0.96 (95%CI 0.96 to 0.97), respectively.
Interpretation: Maintenance of skin and axillary temperature of stable preterm infants in LCI along with kangaroo mother care was non-inferior to SSI, but at a higher incubator temperature by 0.7 °C. No adverse events occurred and LCI had excellent reliability to maintained set-temperature.

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The role of a neonatal hypothermia alert device in promoting weight gain in LBW infants

Mohammad Azad[1], Surender Singh Bisht[1], Amita Tyagi[1], M L Jaipal[1]

Abstract
Background: Neonatal hypothermia is a significant risk factor for preterm and low birth weight (LBW) newborns, especially in India. Kangaroo Mother Care (KMC) is one recommended method of thermal control. A wearable device, TempWatch, has been developed to monitor for and detect hypothermia and to promote KMC for preterm and LBW infants.

Purpose: This randomized controlled trial was designed to evaluate TempWatch's impact on weight gain, amount of KMC received, and length of hospital stay for LBW infants as compared to standard care.
Methods: Otherwise healthy LBW infants (with birthweights 1500-2300 g) admitted to a KMC ward of a government hospital in New Delhi, India were randomly allocated to a TempWatch group or a control group and wore the device until their time of discharge. 50 infants were enrolled in each group. All participants received standard-of-care temperature monitoring, and those in the control group were monitored using the hand-touch method. Each group also received sixth-hourly temperature monitoring. Infants' daily weight and the number of hypothermia episodes they experienced per day were recorded, and mothers of infants in both groups completed daily KMC diaries.
Results: The TempWatch group experienced statistically significant weight gain as compared to the control group (0.06 vs. 0.02 kg, $p = .024$). There were no statistically significant differences between the groups in the number of hypothermia events detected, the amount of KMC received.
Conclusion: TempWatch promotes statistically significant weight gain for LBW infants as compared to standard care.

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Embrace versus Cloth Wrap in preventing neonatal hypothermia during transport: a randomized trial

Vallaree Anant Morgaonkar[1], Dipen Vasudev Patel[2], Ajay Gajanan Phatak[3], Archana Somashekhar Nimbalkar[4], Somashekhar Marutirao Nimbalkar[5]

Abstract
Background: We assessed the efficacy of Embrace Nest Infant Warmer versus Cloth Wrap in preventing hypothermia during short-term transport from the emergency department (ED) to the neonatal intensive care unit (NICU).
Methods: Neonates weighing ≥1500 g coming to the ED were randomized for transport to the NICU. Axillary temperature was measured.
Results: A total of 120 newborns (60 per group) were enrolled. From ED exit to NICU entry, the mean (SD) temperature increased in the Embrace group by 0.37 °C (0.54), whereas it reduced by 0.38 °C (0.80) in the Cloth group ($p < 0.001$). Hypothermia cases reduced in the Embrace group from 39 (65%) to 21 (35%), while it increased from 21 (35%) to 39 (65%) in the Cloth group ($p = 0.001$) from ED exit to NICU entry. The thermoregulation for 24 h after admission to the NICU was superior in the Embrace group.
Conclusions: Embrace showed significantly better thermoregulation in neonates. Further studies should be done to measure its effectiveness in different environments and distances.

Feeding of very low birth weight infants

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Fortification of Breast Milk With Preterm Formula Powder vs Human Milk Fortifier in Preterm Neonates: A Randomized Noninferiority Trial

Arunambika Chinnappan[1], Akash Sharma[1], Ramesh Agarwal[1], Anu Thukral[1], Ashok Deorari[1], M Jeeva Sankar[1]

Abstract

Importance: Fortification of expressed breast milk (EBM) using commercially available human milk fortifiers (HMF) increases short-term weight and length in preterm very low-birth-weight (VLBW) neonates. However, the high cost and increased risk of feed intolerance limit their widespread use. Preterm formula powder fortification (PTF) might be a better alternative in resource-limited settings.

Objective: To demonstrate that fortification of EBM by preterm formula powder is noninferior to fortification by HMF, in terms of short-term weight gain, in VLBW neonates.

Design, setting, and participants: Open-label, noninferiority, randomized trial conducted from December 2017 to June 2019 at a level 3 neonatal unit in India. The trial enrolled preterm (born at or before 34 weeks of gestation) VLBW neonates receiving at least 100 mL/kg/d of feeds and consuming 75% of milk or more as EBM.

Interventions: Neonates were randomly assigned to receive fortification by either PTF or HMF. Calcium, phosphorus, iron, vitamin D, and multivitamins were supplemented in PTF and only vitamin D in the HMF group to meet the recommended dietary allowances.

Main outcomes and measures: The primary outcome was the weight gain until discharge from the hospital or 40 weeks' postmenstrual age, whichever was earlier; the prespecified noninferiority margin was 2 g/kg/d. Secondary outcomes included morbidities such as necrotizing enterocolitis, feed intolerance, and extrauterine growth restriction (<10th percentile on the Fenton chart at 40 weeks' postmenstrual age).

Results: Of the 123 neonates enrolled, 60 and 63 were randomized to the PTF and HMF groups, respectively. The mean gestation (30.5 vs 29.9 weeks) and birth weight (1161 vs 1119 g) were comparable between the groups. There was no difference in the mean (SD) weight gain between the PTF and HMF groups (15.7 [3.9] vs 16.3 [4.0] g/kg/d; mean difference, -0.5 g/kg/d; 95% CI, -1.9 to 0.7). The lower bound of 95% CI did not cross the noninferiority margin. The incidence of feed intolerance was lower in the PTF group (1.4 vs 6.8 per 1000 patient-days; incidence rate ratio 0.19; 95% CI, 0.04 to 0.95), and fewer neonates required withholding of fortification for 24 hours or more (5% vs 22%; risk ratio, 0.22; 95% CI, 0.07 to 0.75). The incidence of necrotizing enterocolitis stage II or more (0 vs 5%) and extrauterine growth restriction (73% vs 81%) was comparable between the groups.

Conclusions and relevance: Fortification with preterm formula powder is not inferior to fortification with human milk fortifiers in preterm neonates. Given the possible reduction in feed intolerance and lower costs, preterm formula might be a better option for fortification, especially in resource-restricted settings.

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Fortification of Human Milk With Infant Formula for Very Low Birth Weight Preterm Infants: A Systematic Review

Manish Kumar[1], Jaya Upadhyay[2], Sriparna Basu[3]

Abstract

Background: Off-label fortification of expressed human milk (HM) with infant milk formula (IMF) is common in developing countries, though its benefits and safety are unclear.

Objective: To study the effects of IMF fortification of HM on growth of very low birth weight (VLBW) preterm infants.

Design: Systematic review and meta-analysis of randomized and quasi-randomized controlled trials (RCTs).

Data sources and selection criteria: MEDLINE, EMBASE, CINAHL, CENTRAL and other databases were searched for articles published in English language from inception to December 2019, evaluating the effects of HM fortified with IMF as intervention, compared to unfortified HM or HM fortified with human milk fortifier (HMF).

Participants: Five RCTs including 423 VLBW preterm infants.

Intervention: Feeding with HM fortified with IMF compared to unfortified or HMF-fortified HM.

Outcome measures: Primary outcome measure was assessment of growth as weight, length and head circumference (HC) gain velocity. Secondary outcome measures were incidences of feed intolerance (FI), necrotizing enterocolitis (NEC), time to reach full feeds, concentration of nutritional biomarkers, duration of hospital-stay and cost of intervention.

Results: Of the five studies included in the review, pooled effects regarding weight gain velocity (SMD 0.27 g/day; 95% CI 0.08 to 0.62), length gain (MD 0.07cm/week; 95% CI 0.02 to 0.16) and HC gain (MD 0.05 cm/wk; 95% CI 0.01 to 0.11), were not statistically significant. Sensitivity analysis by pooling studies using unfortified milk as comparator yielded a statistically significant result for all growth parameters. Risk of FI or NEC was comparable. Length of hospitalstay was reduced in the intervention group.

Conclusions: A very-low quality evidence suggested that IMF fortification of HM is superior to unfortified milk and may be a safe alternative for HMF for short term growth of VLBW preterm infants.

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doi: 10.1002/14651858.CD013392.pub2.

Early fortification of human milk versus late fortification to promote growth in preterm infants

Sivam Thanigainathan[1], Thangaraj Abiramalatha[2]

Abstract

Background: Uncertainty exists about the optimal point at which multi-component fortifier should be added to human milk for promoting growth in preterm infants. The most common practice is to start fortification when the infant's daily enteral feed volume reaches 100 mL/kg body weight. Another approach is to commence fortification earlier, in some cases as early as the first enteral feed. Early fortification of human milk could increase nutrient intake and growth rates but may increase the risk of feed intolerance and necrotising enterocolitis (NEC).

Objectives: To assess effects on growth and safety of early fortification of human milk versus late fortification in preterm infants To assess whether effects vary based upon gestational age (≤ 27 weeks; 28 to 31 weeks; ≥ 32 weeks), birth weight (< 1000 g; 1000 to 1499 g; ≥ 1500 g), small or appropriate for gestational age, or type of fortifier (bovine milk-based human milk fortifier (HMF); human milk-based HMF; formula powder) SEARCH METHODS: We used the standard strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 8); OVID MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) (1946 to 15 August 2019); MEDLINE via PubMed (1 August 2018 to 15 August 2019) for the previous year; and the Cumulative Index to Nursing and Allied Health Literatue (CINAHL) (1981 to 15 August 2019). We searched clinical trials databases and reference lists of included studies.
Selection criteria: We included randomised controlled trials that compared early versus late fortification of human milk in preterm infants. We defined early fortification as fortification started at < 100 mL/kg/d enteral feed volume or < 7 days postnatal age, and late fortification as fortification started at ≥ 100 mL/kg/d feeds or ≥ 7 days postnatal age.
Data collection and analysis: Both review authors assessed trial eligibility and risk of bias and independently extracted data. We analysed treatment effects in individual trials, and we reported risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We used the GRADE approach to assess the certainty of evidence.
Main results: We included two trials with a total of 237 infants. All participants were very low birth weight infants (birth weight < 1500 g). Early fortification was started at 20 mL/kg/d enteral feeds in one study and 40 mL/kg/d in the other study. Late fortification was started at 100 mL/kg/d feeds in both studies. One study used bovine milk-based fortifier, and the other used human milk-based fortifier. Meta-analysis showed that early fortification may have little or no effect on growth outcomes including time to regain birth weight (MD -0.06 days, 95% CI -1.32 to 1.20 days), linear growth (MD 0.10 cm/week, 95% CI -0.03 to 0.22 cm/week), or head growth (MD -0.01 cm/week, 95% CI -0.07 to 0.06 cm/week) during the initial hospitalisation period. Early fortification may have little or no effect on the risk of NEC (MD -0.01, 95% CI -0.07 to 0.06). The certainty of evidence was low for these outcomes due to risk of bias (lack of blinding) and imprecision (small sample size). Early fortification may have little or no effect on incidence of surgical NEC, time to reach full enteral feeds, extrauterine growth restriction at discharge, proportion of infants with feed interruption episodes, duration of total parenteral nutrition (TPN), duration of central venous line usage, or incidence of invasive infection, all-cause mortality, and duration of hospital stay. The certainty of evidence was low for these outcomes due to risk of bias (lack of blinding) and imprecision (small sample size). We did not have data for other outcomes such as subsequent weight gain after birth weight is regained, parenteral nutrition-associated liver disease, postdischarge growth, and neurodevelopmental outcomes.
Authors' conclusions: Available evidence is insufficient to support or refute early fortification of human milk in preterm infants. Further large trials would be needed to provide data of sufficient quality and precision to inform policy and practice.

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Macrolides for the prevention and treatment of feeding intolerance in preterm low birth weight infants: a systematic review and meta-analysis

Sriparna Basu[1], Susan Smith[2]

Abstract

The role of macrolides for the prevention and treatment of feeding intolerance (FI) in preterm low birth weight (LBW) infants has not been well established. To assess the efficacy and safety of macrolides to prevent or treat FI in preterm LBW infants. A systematic review and meta-analysis (PROSPERO ID: CRD42020170519) was conducted for English articles published since inception to March 2020, using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register. Search terms included preterm low birth weight infants, macrolides, erythromycin, azithromycin, clarithromycin, and feeding intolerance. Randomized controlled trials (RCTs) assessing the effects of macrolide therapy on the time to achieve full enteral feeding (FEF;150 mL/kg/day), duration of parenteral nutrition (PN), hospitalization, and adverse events in preterm LBW infants were included. Independent extraction of data was done by both authors using predefined data-sheet. Very-low to low-quality evidence from 21 RCTs, 19 for erythromycin (prophylaxis-6, rescue-13) and 2 for clarithromycin (prophylaxis-1, rescue-1) demonstrated a significantly beneficial role of erythromycin for an earlier FEF, both as a prophylaxis (SMD-0.53, 95% CI - 0.74,- 0.33; 6 studies, n = 368) as well as rescue (SMD-1.16, 95% CI - 1.88, - 0.44; 11 studies, n = 664). Rescue therapy was also beneficial for a significant reduction in the duration of PN, hospitalization, incidences of sepsis, necrotizing enterocolitis, and cholestasis. No arrhythmia or infantile hypertrophic pyloric stenosis was reported.Conclusions: Erythromycin therapy, both as prophylaxis and rescue, is beneficial to reduce the time to achieve FEF in preterm LBW infants, at no higher risk of adverse events.

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Two-hourly vs Three-hourly Feeding in Very Low Birthweight Neonates: A Randomized Controlled Trial

Anita Yadav[1], Nausheen Siddiqui[1], Pradeep Kumar Debata[2]

Abstract

Background: There is no consensus regarding the feeding interval in very low birth weight (VLBW) babies. If 2-hourly feeding schedule is feasible without increasing harm to the neonate, the nursing time consumed in the feeding of VLBW babies can be reduced.
Objective: To study whether 3-hourly feeding is non-inferior to 2-hourly feeding with respect to time to reach full feeds in VLBW neonates.
Design: Open-label, randomized controlled trial.
Subjects: 350 Neonates weighing between 1000 to 1500 grams, in whom feed could be started within 96 hours of life randomized to either 2-hourly or 3-hourly feeding schedule.
Primary outcome: Time to achieve full enteral feed.
Results: The primary outcome of time to achieve full enteral feed was comparable in the two feeding schedule groups (median 5 days IQR 4-6 days in both groups; P=0.665). Among the secondary outcomes, there were no significant differences in incidence of hypoglycemia (RR

0.86; 95% CI: 0.29-2.5) feed intolerance (RR 1.08: 95% CI: 0.5-2.3), and necrotizing enterocolitis (RR 0.8; 95% CI: 0.22-2.3) in both the groups.
Conclusions: Three hourly feeding does not increase the risk of hypoglycemia, necrotizing enterocolitis or feed intolerance.

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High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants

Thangaraj Abiramalatha[1], Niranjan Thomas[2], Sivam Thanigainathan[3]

Abstract

Background: Human milk is the best enteral nutrition for preterm infants. However, human milk, given at standard recommended volumes, is not adequate to meet the protein, energy, and other nutrient requirements of preterm or low birth weight infants. One strategy that may be used to address the potential nutrient deficits is to give a higher volume of enteral feeds. High volume feeds may improve nutrient accretion and growth, and in turn may improve neurodevelopmental outcomes. However, there are concerns that high volume feeds may cause feed intolerance, necrotising enterocolitis, or complications related to fluid overload such as patent ductus arteriosus and chronic lung disease. This is an update of a review published in 2017.
Objectives: To assess the effect on growth and safety of high versus standard volume enteral feeds in preterm or low birth weight infants. In infants who were fed fortified human milk or preterm formula, high and standard volume feeds were defined as > 180 mL/kg/day and ≤ 180 mL/kg/day, respectively. In infants who were fed unfortified human milk or term formula, high and standard volume feeds were defined as > 200 mL/kg/day and ≤ 200 mL/kg/day, respectively.
Search methods: We used the standard search strategy of Cochrane Neonatal to search Cochrane Central Register of Controlled Trials (CENTRAL; 2020 Issue 6) in the Cochrane Library; Ovid MEDLINE (1946 to June 2020); Embase (1974 to June 2020); and CINAHL (inception to June 2020); Maternity & Infant Care Database (MIDIRS) (1971 to April 2020); as well as previous reviews, and trial registries.
Selection criteria: We included randomised controlled trials (RCTs) that compared high versus standard volume enteral feeds for preterm or low birth weight infants.
Data collection and analysis: Two review authors assessed trial eligibility and risk of bias and independently extracted data. We analysed treatment effects in individual trials and reported risk ratio (RR) and risk difference for dichotomous data, and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We used the GRADE approach to assess the certainty of evidence. The primary outcomes were weight gain, linear and head growth during hospital stay, and extrauterine growth restriction at discharge.
Main results: We included two new RCTs (283 infants) in this update. In total, we included three trials (347 infants) in this updated review. High versus standard volume feeds with fortified human milk or preterm formula Two trials (283 infants) met the inclusion criteria for this comparison. Both were of good methodological quality, except for lack of masking. Both trials were performed in infants born at < 32 weeks' gestation. Meta-analysis of data from both trials showed high volume feeds probably improves weight gain during hospital stay (MD 2.58 g/kg/day, 95% CI 1.41 to 3.76; participants = 271; moderate-certainty evidence).

High volume feeds may have little or no effect on linear growth (MD 0.05 cm/week, 95% CI -0.02 to 0.13; participants = 271; low-certainty evidence), head growth (MD 0.02 cm/week, 95% CI -0.04 to 0.09; participants = 271; low-certainty evidence), and extrauterine growth restriction at discharge (RR 0.71, 95% CI 0.50 to 1.02; participants = 271; low-certainty evidence). We are uncertain of the effect of high volume feeds with fortified human milk or preterm formula on the risk of necrotising enterocolitis (RR 0.74, 95% CI 0.12 to 4.51; participants = 283; very-low certainty evidence). High versus standard volume feeds with unfortified human milk or term formula One trial with 64 very low birth weight infants met the inclusion criteria for this comparison. This trial was unmasked but otherwise of good methodological quality. High volume feeds probably improves weight gain during hospital stay (MD 6.2 g/kg/day, 95% CI 2.71 to 9.69; participants = 61; moderate-certainty evidence). The trial did not provide data on linear and head growth, and extrauterine growth restriction at discharge. We are uncertain as to the effect of high volume feeds with unfortified human milk or term formula on the risk of necrotising enterocolitis (RR 1.03, 95% CI 0.07 to 15.78; participants = 61; very low-certainty evidence).
Authors' conclusions: High volume feeds (≥ 180 mL/kg/day of fortified human milk or preterm formula, or ≥ 200 mL/kg/day of unfortified human milk or term formula) probably improves weight gain during hospital stay. The available data is inadequate to draw conclusions on the effect of high volume feeds on other growth and clinical outcomes. A large RCT is needed to provide data of sufficient quality and precision to inform policy and practice.

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doi: 10.1007/s12098-021-03778-6. Online ahead of print.
Early Total Versus Gradually Advanced Enteral Nutrition in Stable Very-Low-Birth-Weight Preterm Neonates: A Randomized, Controlled Trial
Mamta Jajoo[1], Amitabh Singh[2], Neha Arora[3], Vikram Bhaskar[3], Anirban Mandal[4]
Abstract
Objective: To assess whether early total enteral nutrition (80 mL/kg/d) started on day 1 of life in hemodynamically stable preterm very-low-birth-weight (VLBW) neonates with the rapid advancement of feeds (20 mL/kg/d) help in the earlier achievement of full feeds (180 mL/kg/d).
Methods: Early total enteral nutrition (intervention) group feeding was started with 80 mL/kg/d on the first day in all hemodynamically stable neonates admitted with birth weight of 1000-1499 grams, born at 29-33 wk of gestation as determined by first-trimester ultrasonography (USG) or expanded New Ballard Score (NBS) and was advanced by 20 mL/kg/d until maximum feeds of 180 mL/kg/d were achieved; while in control group feeding was started with 30 mL/kg/d on the first day and was advanced by 20 mL/kg/d until maximum feeds were achieved. Primary outcome measure was time taken to achieve full feeds; secondary outcomes were duration of hospital stay, necrotizing enterocolitis (NEC), time to regain birth weight, duration of antibiotics, and death.
Results: Sixty VLBW neonates (1000-1499 g) with comparable baseline demographics were randomized within 24 h of admission to two groups. Early total enteral nutrition intervention group (group I, n = 31) achieved the target of full enteral nutrition at median 6 d; IQR: 0 to 7.8

d, a significantly shorter time compared to the controls (n = 29) (median 10 d; IQR: 9 to 11.0 d; p = < 0.05).
Conclusion: Early total enteral nutrition started from the first day of life results in significantly less time to achieve full feeds in hemodynamically stable preterm and VLBW infants.

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Early full enteral feeding for preterm or low birth weight infants
Verena Walsh[1], Jennifer Valeska Elli Brown[2], Bethany R Copperthwaite[3], Sam J Oddie[4], William McGuire[1]
Abstract
Background: The introduction and advancement of enteral feeds for preterm or low birth weight infants is often delayed because of concerns that early full enteral feeding will not be well tolerated or may increase the risk of necrotising enterocolitis. Early full enteral feeding, however, might increase nutrient intake and growth rates; accelerate intestinal physiological, metabolic, and microbiomic postnatal transition; and reduce the risk of complications associated with intravascular devices for fluid administration. OBJECTIVES: To determine how early full enteral feeding, compared with delayed or progressive introduction of enteral feeds, affects growth and adverse events such as necrotising enterocolitis, in preterm or low birth weight infants.
Search methods: We used the standard search strategy of Cochrane Neonatal to search Cochrane Central Register of Controlled Trials; MEDLINE Ovid, Embase Ovid, Maternity & Infant Care Database Ovid, the Cumulative Index to Nursing and Allied Health Literature, and clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials to October 2020.
Selection criteria: Randomised controlled trials that compared early full enteral feeding with delayed or progressive introduction of enteral feeds in preterm or low birth weight infants.
Data collection and analysis: We used the standard methods of Cochrane Neonatal. Two review authors separately assessed trial eligibility, evaluated trial quality, extracted data, and synthesised effect estimates using risk ratios (RR), risk differences, and mean differences (MD) with 95% confidence intervals (CI). We used the GRADE approach to assess the certainty of evidence.
Main results: We included six trials. All were undertaken in the 2010s in neonatal care facilities in India. In total, 526 infants participated. Most were very preterm infants of birth weight between 1000 g and 1500 g. Trials were of good methodological quality, but a potential source of bias was that parents, clinicians, and investigators were not masked. The trials compared early full feeding (60 mL/kg to 80 mL/kg on day one after birth) with minimal enteral feeding (typically 20 mL/kg on day one) supplemented with intravenous fluids. Feed volumes were advanced daily as tolerated by 20 mL/kg to 30 mL/kg body weight to a target steady-state volume of 150 mL/kg to 180 mL/kg/day. All participating infants were fed preferentially with maternal expressed breast milk, with two trials supplementing insufficient volumes with donor breast milk and four supplementing with preterm formula.

Few data were available to assess growth parameters. One trial (64 participants) reported a slower rate of weight gain (median difference -3.0 g/kg/day), and another (180 participants) reported a faster rate of weight gain in the early full enteral feeding group (MD 1.2 g/kg/day). We did not meta-analyse these data (very low-certainty evidence). None of the trials reported rate of head circumference growth. One trial reported that the mean z-score for weight at hospital discharge was higher in the early full enteral feeding group (MD 0.24, 95% CI 0.06 to 0.42; low-certainty evidence). Meta-analyses showed no evidence of an effect on necrotising enterocolitis (RR 0.98, 95% CI 0.38 to 2.54; 6 trials, 522 participants; I^2 = 51%; very low-certainty evidence).

Authors' conclusions: Trials provided insufficient data to determine with any certainty how early full enteral feeding, compared with delayed or progressive introduction of enteral feeds, affects growth in preterm or low birth weight infants. We are uncertain whether early full enteral feeding affects the risk of necrotising enterocolitis because of the risk of bias in the trials (due to lack of masking), inconsistency, and imprecision.

Mymensingh Med J. 2020 Jul;29(3):638-645.

Early Versus Delayed Enteral Feeding for Achieving Full Feeding in Preterm Growth-Restricted Infants: A Randomized Clinical Trial

F Ahmed[1], S K Dey, M Shahidullah, M A Mannan, A Y Raj, S Sharmin

Abstract

Optimal enteral nutrition is essential for growth restricted preterm infants because if nutrition remains suboptimal during early days of life, physical and neuro-developmental outcome might be in danger. However, chronic hypoxia during antenatal period makes them susceptible for feeding intolerance and necrotising enterocolitis during post natal period. So this randomized clinical trial was conducted in the department of Neonatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2018 to June 2019; to evaluate the effect of early versus delayed enteral feeding on preterm growth-restricted infants. During the study period, out of 127 infants with small for gestational age, 50 babies were enrolled and randomly assigned to either early feeding group (n=25) or late feeding group (n=25). Clinical characteristics at trial entry were well balanced between groups. Newborn enrolled in early feeding group reached full feed significantly faster than late feeding group (p=0.001; Hazard ratio 1.24). Early feeding group regained birth weight faster; experienced lesser incidence of neonatal sepsis, experienced less number of feed intolerance, had shorter mean duration of hospital stay and achieved higher weight on post natal age 16th days. All values were statistically significant. Early enteral feeding found to be safe and beneficial in reducing the time to reach full enteral feeding and better weight gain in growth restricted preterm infants.

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doi: 10.1007/s00431-021-04122-y. Online ahead of print.

Routine prefeed gastric aspiration in preterm infants: a systematic review and meta-analysis

Jogender Kumar[1], Jitendra Meena[1], Piyush Mittal[1], Jeeva Shankar[2], Praveen Kumar[3], Arvind Shenoi[4]

Abstract

Despite lack of evidence, the practice of routine prefeed gastric residue aspiration before the next feed is common. Recent studies suggest that this practice might be even harmful. Therefore, we aimed to evaluate the effect of avoiding routine prefeed gastric residue aspiration as compared to routine aspiration, on various clinical outcomes in preterm infants. We searched five different electronic databases (MEDLINE, EMBASE, Web of Science, CINAHL, and Cochrane Library) until March 8, 2021. Only randomized controlled trials comparing the practice of routine prefeed gastric aspiration with no routine aspiration in preterm infants were considered eligible. The random-effects meta-analysis was done using RevMan 5.3 software. Of the 894 unique records identified by our search, we included 6 studies (451 participants) in the review. There was no significant difference in the incidence of necrotizing enterocolitis (RR 0.80; 95% CI 0.31 to 2.08; 421 participants in 5 trials). Avoiding routine prefeed aspiration was associated with achieving full enteral feeds earlier (MD - 3.19 days, 95% CI - 4.22 to - 2.16), shorter duration of hospitalization (MD - 5.32 days; 95% CI - 10.25 to - 0.38), and lower incidence of late-onset sepsis (RR 0.77; 95% CI 0.60 to 0.99). Time to regain birth weight, days of total parenteral nutrition or central venous line usage, culture-positive sepsis, and all-cause mortality did not differ between the two groups.Conclusion: In the absence of other signs of feed intolerance, routine prefeed gastric residue aspiration should be avoided in preterm infants.

Timing of cord clamping in preterm neonates

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doi: 10.1080/14767058.2020.1836148. Online ahead of print.

Delayed cord clamping for prevention of intraventricular hemorrhage in preterm neonates: a randomized control trial

Fariba Hemmati[1], Deepak Sharma[2], Bahia Namavar Jahromi[3], Leila Salarian[4], Nazanin Farahbakhsh[5]

Abstract

Background: Intraventricular hemorrhage (IVH) is a common condition in preterm neonates and is responsible for substantial adverse neurodevelopmental outcome in preterm neonates. Prevention of IVH is an important intervention for better neurological outcome in these preterm neonates.

Aims and objective: This study aimed to determine whether delayed cord clamping (DCC) was superior to immediate cord clamping (ICC) for the prevention of IVH in preterm neonates.

Patients and methods: In this two centered prospective double-blind randomized controlled trial, eligible neonates with gestational age from 26 to 34 weeks were randomized to receive either ICC (cord clamped in 10-15 s) or DCC (cord clamped in 30-45 s) groups. The grading and severity of IVH were evaluated by cranial ultrasound scan done on the 3-4th and 7-10th days after birth.

Results: Among the 148 enrolled neonates, 79 were in the ICC group and 69 were in the DCC group. There was no difference in maternal and neonatal baseline characteristics except the neonates in the DCC group weighed more (ICC 1528.77 ± 365.5 g vs. DCC 1658.11 ± 419.52 g; p = .047) at birth. There was no significant difference in the incidence of any grade of IVH in both groups (ICC 12.8% vs. DCC 14.5%; p = .745). There was a significantly higher incidence of grade I IVH (ICC 2.5% vs. DCC 13%; p = .024) in the DCC group. The incidence of grade II IVH (ICC 5.1% vs. DCC 0%; p = .123); grade III IVH (ICC 3.8% vs. DCC 1.4%; p = .623); and grade IV IVH (ICC 1.3% vs. DCC 0%; p>.999) were comparable between the two groups. The incidence of a significant IVH (grades II, III, and IV) was significantly less in the DCC group (ICC 10.1% vs. DCC 1.4%, p = .036). The mean initial hemoglobin levels were significantly higher in neonates enrolled in DCC (15.41 ± 2.1 vs. 16.46 ± 2.45 g/dL; p = .007). There was a significant reduction in the number of days of hospital stay (ICC 18.78 ± 15.42 vs. DCC 13.21 ± 16.16; p = .002). There was no difference in initial hematocrit, platelet count, maximum bilirubin level, and Apgar score (p>.05).
Conclusions: Although there was no reduction in any grade of IVH, the incidence of significant IVH (grades II, III, and IV) was significantly decreased with the use of DCC in preterm neonates. Delayed cord clamping also resulted in a significant increase in birth weight, higher hemoglobin levels, and shorter hospital stays without any increase in the risks of hyper-bilirubinemia, low Apgar score, and neonatal mortality.

Lancet Glob Health. 2020 Aug;8(8):e1061-e1070.
doi: 10.1016/S2214-109X(20)30232-1.

Effect of a quality improvement package for intrapartum and immediate newborn care on fresh stillbirth and neonatal mortality among preterm and low-birthweight babies in Kenya and Uganda: a cluster-randomised facility-based trial

Dilys Walker[1], Phelgona Otieno[2], Elizabeth Butrick[3], Gertrude Namazzi[4], Kevin Achola[2], Rikita Merai[3], Christopher Otare[2], Paul Mubiri[4], Rakesh Ghosh[3], Nicole Santos[3], Lara Miller[3], Nancy L Sloan[3], Peter Waiswa[5], Preterm Birth Initiative Kenya and Uganda Implementation Research Collaborative

Abstract

Background: Although gains in newborn survival have been achieved in many low-income and middle-income countries, reductions in stillbirth and neonatal mortality have been slow. Prematurity complications are a major driver of stillbirth and neonatal mortality. We aimed to assess the effect of a quality improvement package for intrapartum and immediate newborn care on stillbirth and preterm neonatal survival in Kenya and Uganda, where evidence-based practices are often underutilised.
Methods: This unblinded cluster-randomised controlled trial was done in western Kenya and eastern Uganda at facilities that provide 24-h maternity care with at least 200 births per year. The study assessed outcomes of low-birthweight and preterm babies. Eligible facilities were pair-matched and randomly assigned (1:1) into either the intervention group or the control group. All facilities received maternity register data strengthening and a modified WHO Safe Childbirth Checklist; facilities in the intervention group additionally received provider mentoring using PRONTO simulation and team training as well as quality improvement collaboratives. Liveborn or fresh stillborn babies who weighed between 1000 g and 2500 g, or

less than 3000 g with a recorded gestational age of less than 37 weeks, were included in the analysis. We abstracted data from maternity registers for maternal and birth outcomes. Follow-up was done by phone or in person to identify the status of the infant at 28 days. The primary outcome was fresh stillbirth and 28-day neonatal mortality. This trial is registered with ClinicalTrials.gov, NCT03112018.
Findings: Between Oct 1, 2016, and April 30, 2019, 20 facilities were randomly assigned to either the intervention group (n=10) or the control group (n=10). Among 5343 eligible babies in these facilities, we assessed outcomes of 2938 newborn and fresh stillborn babies (1447 in the intervention and 1491 in the control group). 347 (23%) of 1491 infants in the control group were stillborn or died in the neonatal period compared with 221 (15%) of 1447 infants in the intervention group at 28 days (odds ratio 0·66, 95% CI 0·54-0·81). No harm or adverse effects were found.
Interpretation: Fresh stillbirth and neonatal mortality among low-birthweight and preterm babies can be decreased using a package of interventions that reinforces evidence-based practices and invests in health system strengthening.

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doi: 10.1186/s12889-021-11215-8.

Factors associated with birthweight and adverse pregnancy outcomes among children in rural Guinea-Bissau - a prospective observational study

Alexander Dahl Stjernholm[1 2 3], Sanne Marie Thysen[4 5 6 7], Igualdino Da Silva Borges[2], Ane Bærent Fisker[1 2 3]

Abstract
Background: Low birthweight (LBW) is associated with higher mortality and morbidity, but there is limited data on the prevalence of LBW in rural Africa, where many births occur at home. The Bacillus Calmette-Guérin (BCG) vaccine has non-specific effects. Studies suggest that maternal BCG-vaccination may affect the health of the child.
Methods: The present study is nested within a randomised trial in rural Guinea-Bissau: Pregnancies were registered at two-monthly village visits, where information on BCG scar status and other background factors were obtained. Children were enrolled in the trial and weighed at home within 72 h after birth. In this prospective observational study, we assessed factors associated with adverse pregnancy outcomes and birthweight in binomial and linear regression models.
Results: Among 1320 women who had their BCG scar status assessed, 848 (64%) had a scar, 472 (36%) had no scar. The risk of adverse pregnancy outcomes (miscarriages, stillbirths, early neonatal deaths) tended to be higher among BCG scar-negative women (13%) than among women with a BCG scar (10%), adjusted prevalence ratio = 1.29 (0.99-1.68). Birthweight was assessed for 628 (50%) of the 1232 live born children. The mean birthweight was 2.89 kg (SD 0.43) and the proportion of LBW children was 17% (104/628). Sex, twinning, region of birth, maternal age, maternal mid-upper arm circumference (MUAC), antenatal consultations, parity and possession of a mobile phone were associated with birthweight, while maternal BCG scar status was not.
Conclusions: This study provides the first birthweight data for home-born children in rural Guinea-Bissau, with a mean birthweight of 2.89 kg (SD 0.43) and a LBW prevalence of 17%.

We found a tendency for higher risk of adverse pregnancy outcomes among BCG scar-negative women. Birthweight was similar in children of mothers with and without BCG scar.

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Prophylactic Probiotic Supplementation for Preterm Neonates-A Systematic Review and Meta-Analysis of Nonrandomized Studies

Mangesh Deshmukh[1,2], Sanjay Patole[3,4]

Abstract

Systematic review and meta-analyses of randomized controlled trials (RCTs) show that probiotics reduce the risk of necrotizing enterocolitis (NEC ≥ Stage II), late onset sepsis (LOS), all-cause mortality, and feeding intolerance in preterm neonates. Data from observational studies is important to confirm probiotic effects in clinical practice. We aimed to compare outcomes before and after implementing routine probiotic supplementation (RPS) in preterm neonates (<37 weeks of gestation) by performing a systematic review of non-RCTs using Cochrane methodology. Databases including PubMed, The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Cochrane Central library, and Google Scholar were searched in May 2020. A meta-analysis was performed using a random effects model. Categorical measure of effect size was expressed as OR and 95% CI. Statistical heterogeneity was assessed by the chi-squared test, I2 statistic. The level of evidence (LOE) was summarized using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines. Primary outcomes were NEC ≥ Stage II, LOS, and all-cause mortality. Secondary outcomes included probiotic sepsis. Thirty good-quality non-RCTs (n = 77,018) from 18 countries were included. The meta-analysis showed RPS was associated with significantly reduced: 1) NEC ≥ Stage II (30 studies, n = 77,018; OR: 0.60; 95% CI: 0.50, 0.73; P <0.00001, I2: 65%; LOE: Moderate), 2) LOS: (21 studies, n = 65,858; OR: 0.85; 95% CI: 0.74, 0.97; P = 0.02, I2: 74%; LOE: Low), and 3) all-cause mortality (27 non-RCTs, n = 70,977; OR: 0.77; 95% CI: 0.68, 0.88; P = 0.0001, I2: 49%; LOE: Low). Subgroups: 1) extremely low birth weight (ELBW: birth weight <1000 g) neonates: RPS was associated with significantly reduced NEC ≥ Stage II (4.5% compared with 7.9%). However, there was no difference in LOS and mortality. 2) Multistrain RPS was more effective than single strain. One study reported 3 nonfatal cases of probiotic sepsis. In summary, moderate- to low-quality evidence indicates that RPS was associated with significantly reduced NEC ≥ Stage II, LOS, and all-cause mortality in neonates <37 weeks of gestation and NEC ≥ Stage II in ELBW neonates.

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Factors determining cognitive, motor and language scores in low birth weight infants from North India

Ravi Prakash Upadhyay[1,2], Sunita Taneja[1], Suman Ranjitkar[3], Sarmila Mazumder[1], Nita Bhandari[1], Tarun Dua[4], Laxman Shrestha[3], Tor A Strand[5]

Free article

Abstract

Background: Children born with low birth weight (LBW) tend to have lower neurodevelopmental scores compared to term normal birth weight children. It is important to determine factors that influence neurodevelopment in these low birth weight children especially in the first 2-3 years of life that represents a period of substantial brain development.
Methods: This secondary data analysis was conducted using data from LBW infants enrolled soon after birth in an individually randomized controlled trial (RCT) and followed up till end of 1st year. Neurodevelopmental assessment was done at 12 months of corrected age by trained psychologists using Bayley Scales of Infant and Toddler Development 3rd edition (Bayley-III). Factors influencing cognitive, motor and language scores were determined using multivariable linear regression model.
Results: Linear growth (i.e., length for age z score, LAZ) [cognitive: Standardized ß-coefficient = 2.19, 95% CI; 1.29, 3.10; motor: 2.41, 95% CI; 1.59, 3.23; language: 1.37, 95% CI; 0.70, 2.04], stimulation at home [cognitive: 0.21, 95% CI; 0.15, 0.27; motor: 0.12, 95% CI; 0.07, 0.17; language: 0.21, 95% CI; 0.16, 0.25] and number of diarrhoeal episodes [cognitive: -2.87, 95% CI; -4.34, -1.39; motor: -2.62, 95% CI; -3.93, -1.29; language: -2.25, 95% CI; -3.32, -1.17] influenced the composite scores in all three domains i.e., cognitive, language and motor. While increase in LAZ score and stimulation led to increase in composite scores; an increase in number of diarrhoeal episodes was associated with decrease in scores. Weight for height z scores (WHZ) were associated with motor and language but not with cognitive scores. Additionally, a negative association of birth order with cognitive and language scores was noted.
Conclusions: The findings indicate the possible importance of promoting nutrition and preventing diarrhoea as well as ensuring optimal stimulation and nurturance at home for enhancing child development in LBW infants.

Community care of the very low birth weight baby

BMC Public Health. 2020 Aug 24;20(1):1274.
doi: 10.1186/s12889-020-09317-w.
Community-based cluster randomized controlled trial: empowering households to identify and provide appropriate care for low-birthweight newborns in Nepal
Stephen Hodgins[1], Binamra Rajbhandari[2], Deepak Joshi[3], Bharat Ban[4], Subarna Khatry[4], Luke C Mullany[5]
Abstract
Background: Most newborn deaths occur among those of low birthweight (LBWt), due to prematurity &/or impaired fetal growth. Simple practices can substantially mitigate this risk. In low-income country settings where many births occur at home, strategies are needed that empower mothers to determine if their babies are at higher risk and, if so, to take measures to reduce risk. Earlier studies suggest that foot-length may be a good proxy for birthweight. An earlier Nepal study found a 6.9 cm cut-off performed relatively well, differentiating normal from low birthweight.
Methods: Community-based, cluster-randomized controlled trial.

Objective: to determine whether family-administered screening, associated with targeted messages improves care practices known to mitigate LBWt-associated risks.
Participants: women participating in a parent trial in rural Nepal, recruited late in pregnancy. Women were given a 6.9 cm card to assess whether the baby's foot is small; if so, to call a number on the card for advice. Follow-up visits were made over the 2 weeks following the birth, assessing for 2 behavioral outcomes: reported skin-to-skin thermal care, and care-seeking outside the home; assessed restricting to low birthweight (using 2 cutoffs: 2500 g and 2000 g). Randomization: 17 clusters intervention, 17 control. The study also documented performance along the presumed causal chain from intervention through behavioral impact.
Results: 2022 intervention, 2432 control. Intervention arm: 519 had birthweight < 2500 g (vs. 663 among controls), of which 503 were available for analysis (vs. 649 among controls). No significant difference found on care-seeking; for those < 2500 g RR 1.13 (95%CI: 0.97-1.131). A higher proportion of those in the intervention arm reported skin-to-skin thermal care than among controls; for those < 2500 g RR 2.50 (95%CI: 2.01-3.1). However, process measures suggest this apparent effect cannot be attributed to the intervention; the card performed poorly as a proxy for LBWt, misclassifying 84.5% of those < 2000 as normal weight.
Conclusions: Although the trial found an apparent effect on one of the behavioral outcomes, this cannot be attributed to the intervention; most likely it was a result of pure chance. Other approaches are needed for identifying small, at-risk babies in such settings, and targeting them for appropriate care messaging.

EClinicalMedicine. 2021 Mar 2;33:100762.
doi: 10.1016/j.eclinm.2021.100762. eCollection 2021 Mar.

Effectiveness of antenatal screening of asymptomatic bacteriuria in reduction of prematurity and low birth weight: Evaluating a point-of-care rapid test in a pragmatic randomized controlled study

Manish Gehani[1], Suman Kapur[1], Sudha D Madhuri[2], Vara Prasad Pittala[3], Sree Kala Korvi[4], Nagamani Kammili[2], Shashwat Sharad[5]

Abstract
Background: Premature babies suffer higher mortality and life-long disabilities. Asymptomatic bacteriuria (ASB) is postulated to induce preterm labor. Routine antenatal screening for ASB using urine culture is not feasible in most developing countries due to long turn-around time, user-unfriendliness, and lack of resources. The current parallel-group superiority pragmatic randomized controlled trial evaluated the effect of screening and evidence-based treatment of ASB using an optical-sensor-based point-of-care rapid-test on the incidence of preterm birth and low birthweight (LBW).
Methods: 240 consenting asymptomatic pregnant women visiting an Indian tertiary public hospital for first antenatal check-up, irrespective of trimester/gravida, who had not consumed antibiotics in the preceding week, were enrolled from February-May 2017. Computer-generated concealed simple randomization allocation sequence was used to assign participants to intervention (120) and control arm (120). Usual hospital-care was provided in the control arm. In the intervention arm, urine samples were additionally

screened for ASB using the rapid-test and the positive women were prescribed susceptible antibiotics. Blinded outcome assessors followed up with women post-delivery. The study was registered with the Clinical Trials Registry-India (CTRI/2016/09/007240).
Findings: 213 participants were analyzed (intervention: 103, control: 110). 21 women were found positive for ASB and prescribed pathogen-specific antibiotics. The incidence of preterm birth/LBW in intervention arm (*n* = 27) was lower than control arm (*n* = 45) by 14·7% (95% CI: 2·2-27·2); RR: 0.64, (95% CI: 0·43-0·95); *p* = 0·023, X^2=5·13.
Interpretation: Rapid-test-guided treatment for ASB reduced the incidence of preterm birth/LBW in a pragmatic setting without any adverse event.

Indian J Pediatr. 2021 Feb 24.
doi: 10.1007/s12098-021-03659-y. Online ahead of print.
Duration of Caffeine for Apnea of Prematurity-A Randomized Controlled Trial
Raj Prakash[1], Femitha Pournami[2], Jyothi Prabhakar[1], Anand Nandakumar[1], P M C Nair[1], Naveen Jain[1]
Abstract
Objectives: There is sufficient evidence to support use of caffeine therapy for apnea of prematurity, but practices vary widely when it comes to discontinuing therapy. This study was planned to compare 'recurrence of apnea of prematurity' (RAP); when 2 protocols were used to stop caffeine therapy.
Methods: Neonates delivered at 26-32 wk gestation on caffeine therapy for apnea of prematurity were randomized into 2 groups: Group 1-caffeine stopped at 7 d apnea-free period, and Group 2-continued for a prefixed period till at least 34 wk postmenstrual age (PMA). Proportion of infants in each group with RAP were analyzed.
Results: Each group consisted of 60 infants. Proportion of infants in each group with RAP, were not different (15% vs 13%); odds ratio (OR) 0.87; 95% confidence interval (CI) (0.31-2.43). Caffeine could be stopped earlier (33 vs 34 wk PMA); and cumulative duration of therapy was lesser (19.5 vs 33 d) when stopped at 7 d apnea-free period. Other studied outcomes were similar between the two groups.
Conclusions: Mandatorily continuing caffeine therapy up to 34 wk PMA in select preterm groups does not seem to decrease risk of recurrence of apnea. Larger trials that specifically study extremely preterm infants are required to make robust recommendations on when to stop therapy.

CNS Drugs. 2021 May 6.doi: 10.1007/s40263-021-00817-w. Online ahead of print.
Erythropoietin Improves Poor Outcomes in Preterm Infants with Intraventricular Hemorrhage
Juan Song[#1], Yong Wang[#1], Falin Xu[1], Huiqing Sun[2], Xiaoli Zhang[1], Lei Xia[1], Shan Zhang[1], Kenan Li[1], Xirui Peng[1], Bingbing Li[1], Yaodong Zhang[2], Wenqing Kang[2], Xiaoyang Wang[1 3], Changlian Zhu[4 5 6]
Abstract
Background: Intraventricular hemorrhage (IVH) is a common complication in preterm infants that has poor outcomes, especially in severe cases, and there are currently no widely

accepted effective treatments. Erythropoietin has been shown to be neuroprotective in neonatal brain injury.
Objective: The objective of this study was to evaluate the protective effect of repeated low-dose recombinant human erythropoietin (rhEPO) in preterm infants with IVH.
Methods: This was a single-blinded prospective randomized controlled trial. Preterm infants ≤ 32 weeks gestational age who were diagnosed with IVH within 72 h after birth were randomized to receive rhEPO 500 IU/kg or placebo (equivalent volume of saline) every other day for 2 weeks. The primary outcome was death or neurological disability assessed at 18 months of corrected age.
Results: A total of 316 eligible infants were included in the study, with 157 in the rhEPO group and 159 in the placebo group. Although no significant differences in mortality (p = 0.176) or incidence of neurological disability (p = 0.055) separately at 18 months of corrected age were seen between the rhEPO and placebo groups, significantly fewer infants had poor outcomes (death and neurological disability) in the rhEPO group: 14.9 vs. 26.4%; odds ratio (OR) 0.398; 95% confidence interval (CI) 0.199-0.796; p = 0.009. In addition, the incidence of Mental Development Index scores of < 70 was lower in the rhEPO group than in the placebo group: 7.2 vs. 15.3%; OR 0.326; 95% CI 0.122-0.875; p = 0.026.
Conclusions: Treatment with repeated low-dose rhEPO improved outcomes in preterm infants with IVH.

Brain Sci. 2021 Apr 29;11(5):575.
doi: 10.3390/brainsci11050575.

Preventive Intervention Program on the Outcomes of Very Preterm Infants and Caregivers: A Multicenter Randomized Controlled Trial

Young-Ah Youn[1], Seung-Han Shin[2], Ee-Kyung Kim[2], Hye-Jeong Jin[2], Young-Hwa Jung[2,3], Ju-Sun Heo[4,5], Ji-Hyun Jeon[4], Joo-Hyun Park[6], In-Kyung Sung[1]

Abstract
Increased survival in the very preterm population results in a higher risk of developing neurodevelopmental and behavioral disabilities among survivors. We examined the outcomes of very preterm infants and parents after a preventive intervention program of four home visits by a specialized nurse, 5 days, 2 weeks, and 1 month after discharge, respectively, and at CA 2 months, followed by up to 12 times of group sessions between CA 3 and 6 months. Our multicenter randomized controlled trial assessed 138 preterm infants (gestational age ≤30 weeks or birth weight ≤1500 g) enrolled from the three participating hospitals. We randomly allocated the preterm babies to either the intervention or the control group. The primary outcome was the neurodevelopmental outcomes of Bayley-III scores at CA 10 and 24 months. At CA 10 months and 24 months, there were no significant differences between the intervention and control groups in the cognitive, motor, and language domains of Bayley-III scores. In addition, there were no significant differences in the mother's depression scale, mother-child attachment, and the modified Infant and Toddler Social and Emotional Assessment.

BMJ Glob Health. 2021 Feb;6(2):e003618.
doi: 10.1136/bmjgh-2020-003618.

Evidence-based interventions to reduce mortality among preterm and low-birthweight neonates in low-income and middle-income countries: a systematic review and meta-analysis

Mirjam Y Kleinhout[#1,2], Merel M Stevens[#3], Kwabena Aqyapong Osman[4], Kwame Adu-Bonsaffoh[5,6], Floris Groenendaal[2], Nejimu Biza Zepro[7,8], Marcus J Rijken[5,9], Joyce L Browne[5]

Abstract

Background: Preterm birth is the leading cause of under-five-mortality worldwide, with the highest burden in low-income and middle-income countries (LMICs). The aim of this study was to synthesise evidence-based interventions for preterm and low birthweight (LBW) neonates in LMICs, their associated neonatal mortality rate (NMR), and barriers and facilitators to their implementation. This study updates all existing evidence on this topic and reviews evidence on interventions that have not been previously considered in current WHO recommendations.

Methods: Six electronic databases were searched until 3 March 2020 for randomised controlled trials reporting NMR of preterm and/or LBW newborns following any intervention in LMICs. Risk ratios for mortality outcomes were pooled where appropriate using a random effects model (PROSPERO registration number: CRD42019139267).

Results: 1236 studies were identified, of which 49 were narratively synthesised and 9 contributed to the meta-analysis. The studies included 39 interventions in 21 countries with 46 993 participants. High-quality evidence suggested significant reduction of NMR following antenatal corticosteroids (Pakistan risk ratio (RR) 0.89; 95% CI 0.80 to 0.99|Guatemala 0.74; 0.68 to 0.81), single cord (0.65; 0.50 to 0.86) and skin cleansing with chlorhexidine (0.72; 0.55 to 0.95), early BCG vaccine (0.64; 0.48 to 0.86; I^2 0%), community kangaroo mother care (OR 0.73; 0.55 to 0.97; I^2 0%) and home-based newborn care (preterm 0.25; 0.14 to 0.48|LBW 0.42; 0.27 to 0.65). No effects on perinatal (essential newborn care 1.02; 0.91 to 1.14|neonatal resuscitation 0.95; 0.84 to 1.07) or 7-day NMR (essential newborn care 1.03; 0.83 to 1.27|neonatal resuscitation 0.92; 0.77 to 1.09) were observed after training birth attendants.

Conclusion: The findings of this study encourage the implementation of additional, evidence-based interventions in the current (WHO) guidelines and to be selective in usage of antenatal corticosteroids, to reduce mortality among preterm and LBW neonates in LMICs. Given the global commitment to end all preventable neonatal deaths by 2030, continuous evaluation and improvement of the current guidelines should be a priority on the agenda.

Rapid vs. Slow Rewarming for Management of Moderate to Severe Hypothermia in Low-Birth-Weight Pre-term Neonates-An Open Label Randomized Controlled Trial

Prerana Jain[1], Jagjit Singh Dalal[2], Geeta Gathwala[1]

Abstract

Background: Evidence is lacking regarding the optimal method of rewarming hypothermic low-birth-weight (LBW) pre-term neonates. We aim to evaluate the effect of rapid vs. slow rewarming in the management of moderate to severe hypothermia in LBW pre-term neonates.

Methods: In this open label, randomized controlled trial, 100 LBW (<2.5 kg), pre-term (<37 weeks) neonates with moderate to severe hypothermia (<36°C) was randomized to two groups of 50 each and received either rapid (at >0.5°C/h) or slow (at ≤0.5°C/h) rewarming rate till normothermia. The primary outcome was stabilization score [TOPS (temperature,

oxygenation, perfusion and saturation) and MSNS (modified sick neonatal score)] at baseline, 6 and 24 h and mortality until discharge. Other neonatal morbidities were assessed as secondary outcomes.
Results: Mean TOPS score and MSNS score at baseline, 6 and 24 h of admission as well as change in score from baseline were similar between the two groups. The median rewarming rate [interquartile range (IQR)] was higher in rapid rewarming group than in the slow rewarming group [5.05°C/h (3.54-7.71) vs. 0.71°C/h (0.60-0.90); p < 0.001]. The median rewarming time taken in rapid rewarming group was lesser compared with that in the slow rewarming group [0.31 h (IQR 0.13-0.75) vs. 2.05 h (IQR 1.11-3.03); p < 0.001]. Mortality in rapid rewarming and slow rewarming group was similar [7/50 vs. 5/50; OR 1.46 (0.43-4.97), p = 0.538].
Conclusion: Rapid rewarming was as effective and safe as slow rewarming in the management of moderate to severe hypothermia in LBW pre-term neonates with similar short-term neonatal outcomes.

Biomed Hub. 2021 Jan 18;6(1):17-34.
doi: 10.1159/000512274. eCollection Jan-Apr 2021.
Birthweight and Environmental Conditions Impact Skin Barrier Adaptation in Neonates Receiving Natural Oil Massage
Marty O Visscher[1], Aimee Summers[2], Vivek Narendran[1], Subarna Khatry[3], Jeevan Sherchand[4], Steven LeClerq[2 3], Joanne Katz[2], James Tielsch[5], Luke Mullany[2]
Abstract
Introduction: Skin interventions have been implemented to reduce neonatal mortality, demonstrating the skin's role in neonatal innate immunity. We examined the impact of birthweight and environmental conditions on skin integrity in infants receiving oil massage in rural Nepal.
Methods: In a community-based cluster randomized controlled trial, 991 premature and full-term infants were grouped by birthweight as: (1) 920-1,560 g, (2) 1,570-2,450 g, (3) 2,460-2,990 g, and (4) 3,000-4,050 g and by high or low heat index (HI). Skin integrity was measured as erythema, rash, dryness, pH, protein concentration, and transepidermal water loss (TEWL).
Results: Skin pH was higher for the smallest (group 1) than the largest infants (group 4) and higher for group 2 than 3 and 4. Arm and leg rash differed for all 4 groups, with the least amount of rash for the smallest babies. Erythema was lower for group 1 than all others. The lower day 1 values for pH, TEWL and protein at high versus low HI remained lower over 28 days. The pH reduction was faster at high HI. Erythema (arm, leg) was more severe at high HI. Rash severity was greater at high HI for arms and legs every day.
Conclusions: Birthweight influenced the skin response to oil massage. The smallest infants had the lowermost skin irritation, suggesting diminished ability to mount an inflammatory response. High HI may be protective for premature infants in low resource settings.

BMC Pregnancy Childbirth. 2021 Jan 5;21(1):6.
doi: 10.1186/s12884-020-03502-w.

A randomized controlled clinical trial of the effect of supportive counseling on mental health in Iranian mothers of premature infants

Leila Seiiedi-Biarag[1], Mojgan Mirghafourvand[2], Khalil Esmaeilpour[3], Shirin Hasanpour[4]

Abstract

Background: Premature birth can affect maternal mental health. Considering that the mental health disorder in mothers may play a vital role in the growth and development of their children, therefore, this study was conducted to determine the effect of supportive counseling on mental health (primary outcome), mother-child bonding and infant anthropometric indices (secondary outcomes) in mothers of premature infants.

Methods: This randomized controlled clinical trial was carried out on 66 mothers with hospitalized neonates in the NICU of Alzahra hospital in Tabriz- Iran. Participants were randomly allocated into two groups of intervention (n = 34) and control (n = 32) through a block randomization method. The intervention group received 6 sessions of supportive counseling (45-60 minutes each session) by the researcher, and the control group received routine care. Questionnaires of Goldberg General Health and the postpartum bonding were completed before the intervention (first 72 hours postpartum) and 8 weeks postpartum. Also, the anthropometric index of newborns were measured at the same time.

Results: There was no statistically significant difference between the two groups in terms of socio-demographic characteristics. After the intervention, based on ANCOVA with adjusting the baseline score, mean score of mental health (AMD: -9.8; 95% Confident Interval (95% CI): -12.5 to -7.1; P < 0.001) and postpartum bonding (AMD: -10.0; 95% CI: -0.6 to 13.9; P < 0.001) in the counseling group was significantly lower than those of the control group; however, in terms of weight (P = 0.536), height (P = 0.429) and head circumference (P = 0.129), there was no significant difference between the two groups.

Conclusions: Supportive counseling may improve mental health and postpartum bonding in mothers of premature infants. Thus, it may be recommendable for health care providers to offer it to mothers.

Perinatal asphyxia

J Trop Pediatr. 2021 Jan 29;67(1):fmaa073.
doi: 10.1093/tropej/fmaa073.

Effect of Therapeutic Hypothermia on the Outcome in Term Neonates with Hypoxic Ischemic Encephalopathy-A Randomized Controlled Trial

R Christina Catherine[1], Vishnu Bhat Ballambattu[2], Bethou Adhisivam[1], Shruthi K Bharadwaj[1], Chinnakali Palanivel[3]

Abstract

Objective: To assess the effect of therapeutic hypothermia on the outcome in term neonates with hypoxic ischemic encephalopathy (HIE).

Methods: A randomized controlled trial was conducted in a tertiary care teaching hospital in south India. Term infants with moderate to severe HIE were randomized to be treated with normothermia or hypothermia. Mortality, neurological abnormality or normal outcome was recorded at hospital discharge or 28 days of age, whichever was earlier, and at 18 months of age.

Results: The baseline maternal and neonatal characteristics in the two groups were similar. The 78 infants in the hypothermia group had more normal survivors at discharge (38%) than the 84 infants in the normothermia group (30%), ratio 1.29 (95% confidence interval 0.84-1.99), and at 18 months of age (65% vs. 42%), ratio 1.54 (1.13-2.10). When these results were combined with those of a previous randomized trial in the same neonatal unit, there were significantly more normal survivors with hypothermia compared to normothermia at discharge, ratio 1.49 (1.18-1.88) and at 6-18 months of age, ratio 1.37 (1.17-1.60).
Conclusion: In term infants with HIE, therapeutic hypothermia reduced mortality and neurological abnormalities, and resulted in more normal survivors.
Lay summary: Babies who do not breathe immediately after they are born are likely to die or have brain damage. Previous studies have suggested that cooling these babies after birth might reduce the number who die or have brain damage. In this resource-limited setting, babies who were cooled were less likely to die or survive with brain damage.

Front Neurol. 2020 Jul 16;11:704.
doi: 10.3389/fneur.2020.00704. eCollection 2020.
Birth Asphyxia Is Associated With Increased Risk of Cerebral Palsy: A Meta-Analysis
Shan Zhang[1], Bingbing Li[1], Xiaoli Zhang[1], Changlian Zhu[1 2 3], Xiaoyang Wang[1 4]
Abstract
Objective: To assess the association between birth asphyxia-as defined by the pH of umbilical cord blood-and cerebral palsy in asphyxiated neonates ≥35 weeks' gestation. **Methods:** Two reviewers independently selected English-language studies that included data on the incidence of cerebral palsy in asphyxiated neonates ≥35 weeks' gestation. Studies were searched from the Embase, Google Scholar, PubMed, and Cochrane Library databases up to 31 December 2019, and the references in the retrieved articles were screened. **Results:** We identified 10 studies that met the inclusion criteria for our meta-analysis, including 8 randomized controlled trials and 2 observational studies. According to a random effects model, the pooled rate of cerebral palsy in the randomized controlled trials was 20.3% (95% CI: 16.0-24.5) and the incidence of cerebral palsy in the observational studies was 22.2% (95% CI: 8.5-35.8). Subgroup analysis by treatment for hypoxic ischemic encephalopathy in asphyxiated neonates showed that the pooled rates of cerebral palsy were 17.3% (95% CI: 13.3-21.2) and 23.9% (95% CI: 18.1-29.7) for the intervention group and non-intervention group, respectively. **Conclusion:** Our findings suggest that the incidence of cerebral palsy in neonates (≥35 weeks' gestation) with perinatal asphyxia is significantly higher compared to that in the healthy neonate population. With the growing emphasis on improving neonatal neurodevelopment and reducing neurological sequelae, we conclude that the prevention and treatment of perinatal asphyxia is essential for preventing the development of cerebral palsy.

J Trop Pediatr. 2021 May 17;67(2):fmab009.
doi: 10.1093/tropej/fmab009.
Effect of Music on Outcomes of Birth Asphyxia: A Randomized Controlled Trial

Mithun Chandra Konar[1], Kamirul Islam[1], Archan Sil[1], Kaustav Nayek[1], Kanailal Barik[1]

Abstract

Introduction: Birth asphyxia may cause neuro-developmental impairment in the affected newborns especially those who had hypoxic-ischemic encephalopathy. Music therapy has been observed to help in reducing pain and stress in newborns and improve neurodevelopmental outcome.

Objectives: The objective of this study is to determine the effects of music therapy on the outcomes of birth asphyxia.

Methods: A randomized controlled trial involving 3095 newborns born between January 2013 and August 2019 with birth asphyxia was conducted in the neonatal intensive care unit of Burdwan Medical College. They were distributed in two groups-A (received music therapy along with coventional management) and B (only received conventional management), using computer-generated randomization. Pain score was assessed during any painful procedure and the neurodevelopmental outcome was measured at 3rd, 6th, 12th, 18th and 24th months. $p < 0.01$ was considered statistically significant.

Results: A total of 3095 newborns were included with a mean gestation of 34.3 ± 2.1 weeks and 56.7% of them were male. Mean hospital stay, oxygen dependency, requirement of mechanical ventilation and incidence of apnea were significantly lesser among newborns of group A. Newborns of group B showed a significantly higher mean pain score, whereas newborns in Group A exhibited significantly greater mental and motor neurodevelopmental quotients.

Conclusions: Music therapy was observed to help in reducing hospital stay, oxygen dependency, incidences of apnea, pain during procedures and also resulted in better neurodevelopmental outcome. However, before generalizing the findings, further multi-centric research should be undertaken.

Arch Dis Child Fetal Neonatal Ed. 2021 Jun 10;fetalneonatal-2020-321309.
doi: 10.1136/archdischild-2020-321309. Online ahead of print.

Prediction of outcome from MRI and general movements assessment after hypoxic-ischaemic encephalopathy in low-income and middle-income countries: data from a randomised controlled trial

Karoline Aker[1 2], Niranjan Thomas[3], Lars Adde[4 5], Beena Koshy[6], Miriam Martinez-Biarge[7], Ingeborg Nakken[8], Caroline S Padankatti[6], Ragnhild Støen[4 2]

Abstract

Objective: To evaluate the accuracy of neonatal MRI and general movements assessment (GMA) in predicting neurodevelopmental outcomes in infants with hypoxic-ischaemic encephalopathy (HIE).

Design: Secondary analyses of a randomised controlled trial (RCT).

Setting: Tertiary neonatal intensive care unit in India.

Methods: Fifty infants with HIE were included in an RCT of therapeutic hypothermia (25 cooled and 25 non-cooled). All infants underwent brain MRI at day 5, GMA at 10-15 weeks and outcome assessments including Bayley Scales of Infant and Toddler Development, third

edition, at 18 months. Associations between patterns of brain injury, presence/absence of fidgety movements (FMs) and outcomes were assessed.
Results: Seventeen of 47 (36%) had adverse outcome (5 (21%) cooled vs 12 (52%) non-cooled, p=0.025). Eight infants died (four before an MRI, another three before GMA). Two developed severe cerebral palsy and seven had Bayley-III motor/cognitive composite score <85. Twelve (26%) had moderately/severely abnormal MRI and nine (23%) had absent FMs. The positive predictive value (95% CI) of an adverse outcome was 89% (53% to 98%) for moderate/severe basal ganglia and thalami (BGT) injury, 83% (56% to 95%) for absent/equivocal signal in the posterior limb of the internal capsule (PLIC) and 67% (38% to 87%) for absent FMs. Negative predictive values (95% CI) were 85% (74% to 92%) for normal/mild BGT injury, 90% (78% to 96%) for normal PLIC and 86% (74% to 93%) for present FMs.
Conclusions: Neonatal MRI and GMA predicted outcomes with high accuracy in infants with HIE. The GMA is a feasible low-cost method which can be used alone or complementary to MRI in low-resource settings to prognosticate and direct follow-up.

Neonatal Resuscitation

Indian Pediatr. 2021 Jan 15;58(1):25-29.
Suctioning First or Drying First During Delivery Room Resuscitation: A Randomized Controlled Trial
Ashok Kumar[1], Ravi Prakash Yadav[2], Sriparna Basu[2], T B Singh[3]
Abstract
Objective: To compare the effect of suctioning first or drying first on the composite outcome of hypothermia or respiratory distress in depressed newborns requiring delivery room resuscitation.
Design: Open-label, randomized, parallel-group, controlled trial.
Setting: Delivery room and neonatal intensive care unit of a tertiary-care teaching hospital.
Patients: Depressed newborns (n=154) requiring initial steps of resuscitation at birth.
Intervention: During delivery room resuscitation eligible new-borns were randomly allocated to receive either suctioning first or drying first (77 newborns in each group).
Main outcome measure: Composite incidence of hypothermia at admission or respiratory distress at 6 hours of age.
Results: Both groups were comparable with regard to maternal and neonatal characteristics. Composite outcome was similar in both the groups [46 (59.7%) vs 55 (71.4%)] in suctioning first and drying first, respectively [RR (95% CI), 0.84 (0.66-1.05); P=0.13]. Incidence of hypothermia, respiratory distress at admission and oxygen saturation at 6 hours were also similar. On admission to NICU, hypothermia was observed in 26 (33.8%) neonates in suctioning first group and 33 (42.8%) neonates in drying first group but by one hour of age the proportion of hypothermic neonates was 13 (16.9%) and 14 (18.1%), respectively.

Conclusion: In newborns depressed at birth, the sequence of performing initial steps, whether suctioning first or drying first, had comparable effect on composite outcome of hypothermia at admission or respiratory distress at 6 hours of age.

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doi: 10.1002/14651858.CD012671.pub2.

Tracheal suction at birth in non-vigorous neonates born through meconium-stained amniotic fluid

Sushma Nangia[1], Anu Thukral[2], Deepak Chawla[3]

Abstract

Background: Neonates born through meconium-stained amniotic fluid (MSAF) are at risk of developing meconium aspiration syndrome (MAS). Neonates who are non-vigorous due to intrapartum asphyxia are at higher risk of developing MAS. Clearance of meconium from the airways below the vocal cords by tracheal suction before initiating other steps of resuscitation may reduce the risk of development of MAS. However, conducting tracheal suction may not only be ineffective, it may also delay effective resuscitation, thus prolonging and worsening the hypoxic-ischaemic insult. OBJECTIVES: To evaluate the efficacy of tracheal suctioning at birth in preventing meconium aspiration syndrome and other complications among non-vigorous neonates born through meconium-stained amniotic fluid.

Search methods: We used the standard search strategy of Cochrane Neonatal to search Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 11) in the Cochrane Library; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (1946 to 25 November 2020) for randomised controlled trials (RCTs) and quasi-randomised trials. We also searched clinical trials databases and the reference lists of retrieved articles for RCTs and quasi-randomised trials (up to November 2020).

Selection criteria: We included studies enrolling non-vigorous neonates born through MSAF, if the intervention being tested included tracheal suction at the time of birth with an intent to clear the trachea of meconium before regular breathing efforts began. Tracheal suction could be performed with an endotracheal tube or a wide-gauge suction catheter. Neonates in the control group should have been resuscitated at birth with no effort made to clear the trachea of meconium.

Data collection and analysis: Two review authors independently assessed trial quality and extracted data, consulting with a third review author about any disagreements. We used standard Cochrane methodological procedures, including assessment of risk of bias for all studies. Our primary outcomes were: MAS; all-cause neonatal mortality; and incidence of hypoxic-ischaemic encephalopathy (HIE). Secondary outcomes included: need for mechanical ventilation; incidence of pulmonary air leaks; culture-positive sepsis; and persistent pulmonary hypertension. We used the GRADE approach to assess the certainty of evidence.

Main results: We included four studies (enrolling 581 neonates) in the review. All four studies were conducted in tertiary care hospitals in India. Three of the four studies included neonates born at and beyond term gestation, whereas one included neonates born at and beyond 34 weeks of gestation. Due to the nature of the intervention, it was not possible to blind the healthcare personnel conducting the intervention. Tracheal suction compared to

no suction in non-vigorous neonates born through MSAF In non-vigorous infants, no differences were noted in the risks of MAS (RR 1.00, 95% CI 0.80 to 1.25; RD 0.00, 95% CI -0.07 to 0.08; 4 studies, 581 neonates) or all-cause neonatal mortality (RR 1.24, 95% CI 0.76 to 2.02; RD 0.02, 95% CI -0.03 to 0.07; 4 studies, 575 neonates) with or without tracheal suctioning. No differences were reported in the risk of any severity HIE (RR 1.05, 95% CI 0.68 to 1.63; 1 study, 175 neonates) or moderate to severe HIE (RR 0.68, 95% CI 0.43 to 1.09; 1 study, 152 neonates) among non-vigorous neonates born through MSAF. We are also uncertain as to the effect of tracheal suction on other outcomes such as incidence of mechanical ventilation (RR 0.99, 95% CI 0.68 to 1.44; RD 0.00, 95% CI -0.06 to 0.06; 4 studies, 581 neonates), pulmonary air leaks (RR 1.22, 95% CI 0.38 to 3.93; RD 0.00, 95% CI -0.02 to 0.03; 3 studies, 449 neonates), persistent pulmonary hypertension (RR 1.29, 95% CI 0.60 to 2.77; RD 0.02, 95% CI -0.03 to 0.06; 3 studies, 406 neonates) and culture-positive sepsis (RR 1.32, 95% CI 0.48 to 3.57; RD 0.01, 95% CI -0.03 to 0.05; 3 studies, 406 neonates). All reported outcomes were judged as providing very low certainty evidence.
Authors' conclusions: We are uncertain about the effect of tracheal suction on the incidence of MAS and its complications among non-vigorous neonates born through MSAF. One study awaits classification and could not be included in the review. More research from well-conducted large trials is needed to conclusively answer the review question.

Glob Health Action. 2020 Dec 31;13(1):1743496.
doi: 10.1080/16549716.2020.1743496.
Adding video-debriefing to Helping-Babies-Breathe training enhanced retention of neonatal resuscitation knowledge and skills among health workers in Uganda: a cluster randomized trial
Beatrice Odongkara[1 2 3], Thorkild Tylleskär[2], Nicola Pejovic[2 4], Vincentina Achora[1 3 5], David Mukunya[2], Grace Ndeezi[3], James K Tumwine[3], Victoria Nankabirwa[2 3 6]
Abstract
Background: Skilled birth attendants must be competent to provide prompt resuscitation to save newborn lives at birth. Both knowledge and skills (competence) decline with time after training but the optimal duration for refresher training among frontline-skilled birth attendants in low-resource settings is unknown.
Objectives: We assessed the effect of an innovative Helping-Babies-Breathe simulation-based teaching method using video-debriefing compared to standard Helping-Babies-Breathe training on 1) neonatal resuscitation knowledge and skills attainment and 2) competence retention among skilled birth attendants in Northern Uganda.
Methods: A total of 26 health facilities with 86 birth attendants were equally randomised to intervention and control arms. The 2nd edition of the American Association of Pediatrics Helping-Babies-Breathe curriculum was used for training and assessment. Knowledge and skills were assessed pre- and post-training, and during follow-up at 6 months. A mixed effects linear regression model for repeated measures was used to assess the short and long-term effects of the intervention on neonatal resuscitation practices while accounting for clustering.
Results: Eighty-two (95.3%) skilled birth attendants completed follow-up at 6 months. Approximately 80% of these had no prior Helping-Babies-Breathe training and 75% reported practicing neonatal resuscitation routinely. Standard Helping-Babies-Breathe training with

video-debriefing improved knowledge and skills attainment post-training [adjusted mean difference: 5.34; 95% CI: 0.82-10.78] and retention [adjusted mean difference: 2.97; 95% CI: 1.52-4.41] over 6 months post-training compared to standard training after adjusting for confounding and clustering. Factors that reduced knowledge and skills retention among birth attendants were monthly resuscitation of one neonate or more and being in service for more than 5 years.
Conclusion: Adding video-debriefing to standard Helping-Babies-Breathe training had an effect on birth attendants' competence attainment and retention over 6 months in Uganda. However, more research is needed to justify the proposed intervention in this context.

Neonatal seizures

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doi: 10.1016/j.yebeh.2021.107875. Epub 2021 Mar 8.
Effect of early withdrawal of phenobarbitone on the recurrence of neonatal seizures: An open-label randomized controlled trial
Ankush Jindal[1], Suresh Kumar Angurana[2], Renu Suthar[3], Praveen Kumar[4], Venkataseshan Sundaram[4]
Abstract
Background: The long-term administration of phenobarbitone in neonates may be associated with adverse neurological outcome. The timing of stopping phenobarbitone maintenance after acute seizure control in neonates is a matter of debate.
Objectives: To study the effect of early withdrawal of phenobarbitone on recurrence of neonatal seizures.
Study design: Open-label randomized controlled trial.
Participants: Outborn neonates (≥34 weeks of gestation to <28 days of postnatal period) with seizures (n = 221) admitted to Neonatal unit in Pediatric emergency of a tertiary care hospital in north India over 1 year.
Intervention: After a loading dose of phenobarbitone (20 mg/kg), neonates who remained seizure free for at least 12 h were enrolled after written informed consent from parents, and randomized (computer generated block randomization) to 'phenobarbitone withdrawal group' (n = 112) where phenobarbitone maintenance was stopped and 'phenobarbitone continued group' (n = 109) where phenobarbitone maintenance was continued until discharge and further as per clinician's discretion.
Outcomes: The primary outcome was seizure recurrence until discharge and secondary outcomes were time to reach full enteral feeds, duration of hospital stay, abnormal neurological status at discharge, and mortality in two groups.
Results: The baseline variables were comparable in 2 groups. The incidence of seizure recurrence was similar in the phenobarbitone withdrawal and phenobarbitone continued groups (50% vs. 37.6%, respectively, p = 0.078). Among secondary outcomes, the phenobarbitone withdrawal and continued groups had similar time to reach full enteral feeds (4.02 days vs. 4.2 days, p = 0.75), duration of hospital stay (6.3 days vs. 6.5 days, p = 0.23), abnormal neurological status at discharge (45.6% vs. 38%, p = 0.39), and mortality (11.6% vs. 8.3%, p = 0.50).

Conclusion: Early withdrawal of phenobarbitone in neonatal seizures does not lead to a significant increase in the rate of seizure recurrence.

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Efficacy and Safety of Phenobarbitone as First-Line Treatment for Neonatal Seizure: A Systematic Review and Meta-Analysis

Jogender Kumar[1], Jitendra Meena[1], Jaivinder Yadav[1], Lokesh Saini[1]

Abstract

Background and objective: Phenobarbitone is used as a first-line drug for neonatal seizures. However, its poor short- and long-term safety profile is concerning. We aim to systematically synthesize the data on the efficacy and safety of phenobarbitone as a first-line agent and compare it against other anti-epileptic drugs (AEDs) in neonates.

Methods: Using keywords related to the study population (neonatal seizure) and intervention (phenobarbitone), we searched CENTRAL, Embase, PubMed and Web of Science until 15 December 2020. Randomized controlled trials (RCTs) comparing phenobarbitone with any other AED as first-line therapy for seizure control in the neonates were considered eligible. The random-effect meta-analysis was done using RevMan 5.3 software.

Results: We screened through 443 records and identified nine eligible studies (719 participants). Five RCTs comparing phenobarbitone with levetiracetam did not find any difference in seizure control with the first dose [risk ratio (RR) 1.43, 95% CI 0.79-2.57] or adverse effects (RR 4.66; 95% CI 0.33-65.83). Two trials comparing phenobarbitone and phenytoin also did not find any difference in seizure control with the first dose (RR 2.09; 95% CI 0.31-14.03) and other outcomes. Only one RCT compared phenobarbitone and lorazepam and found lorazepam to be more efficacious in seizure control with the first dose (RR 0.71; 95% CI 0.53-0.94). Three trials compared neurodevelopmental outcomes, in which levetiracetam was better in two, whereas one did not find any difference.

Conclusion: Phenobarbitone is at least as efficacious and safe as other drugs like phenytoin and levetiracetam. The data over the long-term neurodevelopmental outcome are lacking. The existing evidence is insufficient to recommend other drugs over phenobarbitone.

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doi: 10.1080/14767058.2020.1844651. Online ahead of print.

Efficacy of Levetiracetam in neonatal seizures: a systematic review

Deepak Sharma[1], Ansar Murtuza Hussain[2], Sweta Shastri Sharma[3]

Abstract

Background: Neonatal seizures represent the most frequent presenting sign of any neurological abnormality secondary to various etiologies in the neonatal period. Phenobarbitone (PB) has been used as first-line anti-epileptic drug in the treatment of seizures but concerns have been raised regarding its neuro-apoptotic effects over the developing brain. Levetiracetam (LEV) is a newer anti-epileptic drug with neuroprotective property and has been used in adults and pediatric patient but its use in neonates have very limited experience. Recently many neonatal studies have sought the role of LEV in the management of neonatal seizures.

Aims and objective: To evaluate the efficacy of Levetiracetam in the management of neonatal seizures.
Search methods: The literature search was done for this systematic review by searching the Cochrane Central Register of Controlled Trials (CENTRAL), and other various electronic databases including PubMed and various sites for ongoing trials and abstracts of conferences.
Results: Two eligible studies were analyzed that fulfilled the inclusion criteria of the systematic review. Fifteen studies were excluded due to the non-fulfillment of inclusion criteria. The primary outcome of both studies was to see the efficiency of LEV in controlling neonatal seizures when compared to PB. Better seizure control after a single loading dose of LEV was seen. Rates of seizure cessation at 24 h was also better in the LEV arm. Neonatal seizures secondary to hypoxic-ischemic encephalopathy (HIE) and receiving therapeutic hypothermia were better controlled with LEV. The side effect of LEV was significantly less when compared to PB.
Conclusion: Levetiracetam has shown to have promising anti-epileptic properties for the management of neonatal seizure with better efficacy and less or no side effects. There is a need to conduct more randomized controlled trials seeking the role of LEV in the acute management of neonatal seizures and also for assessing its neuroprotective role and neurodevelopmental outcome in these neonates.

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Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis

Robert G Hooper[1,2], Viraraghavan Vadakkencherry Ramaswamy[3], Rachael M Wahid[1,2], Prakash Satodia[1,2], Adarsh Bhulani[2]

Abstract
Aim: To assess the effectiveness and safety of levetiracetam when used as first-line treatment of neonatal seizures.
Method: Four electronic databases, Medline, Embase, Web of Science, and ClinicalTrials.gov were systematically searched from inception until 20th November 2020. Randomized controlled trials (RCTs) and observational studies that included neonates born preterm and term were eligible for inclusion. The primary outcome measure was levetiracetam effectiveness, defined as seizure cessation within 24 hours of starting treatment. Secondary outcomes included short-term adverse events, mortality before discharge, and long-term neurodevelopmental outcomes.
Results: Fourteen studies assessing 1188 neonates were included: four RCTs, three observational trials with phenobarbital as the control arm, and seven observational studies of levetiracetam with no control arm. Pooled efficacy of levetiracetam from observational studies was 45% (95% confidence interval [CI] 34-57%) (GRADE - very low). Meta-analysis of RCTs evaluating levetiracetam versus phenobarbital showed that both were equally effective (risk ratio [95% CI] 0.6 [0.30-1.20]) (GRADE - very low). Levetiracetam resulted in a lower risk of short-term adverse events compared to phenobarbital (risk ratio [95% CI] 0.24 [0.06-0.92]) (GRADE - moderate).

Interpretation: Very low certainty of evidence suggests levetiracetam might not be more effective than phenobarbital. Moderate certainty of evidence indicates levetiracetam is associated with a lower risk of adverse events. Future trials on neonatal antiseizure medication therapy should include continuous electroencephalogram (EEG) monitoring as standard of care and enrol a homogenous population with similar seizure aetiology.

Neonatal infection

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IV and oral fosfomycin pharmacokinetics in neonates with suspected clinical sepsis

Zoe Kane[1,2], Silke Gastine[1], Christina Obiero[3], Phoebe Williams[3,4], Sheila Murunga[3], Johnstone Thitiri[3], Sally Ellis[5], Erika Correia[5], Borna Nyaoke[6], Karin Kipper[7], John van den Anker[8,9], Mike Sharland[10], James A Berkley[3,4,11], Joseph F Standing[1,12]

Abstract

Background: Fosfomycin has the potential to be re-purposed as part of a combination therapy to treat neonatal sepsis where resistance to current standard of care (SOC) is common. Limited data exist on neonatal fosfomycin pharmacokinetics and estimates of bioavailability and CSF/plasma ratio in this vulnerable population are lacking.

Objectives: To generate data informing the appropriate dosing of IV and oral fosfomycin in neonates using a population pharmacokinetic analysis of plasma and CSF data.

Methods: The NeoFosfo study (NCT03453177) was a randomized trial that examined the safety and pharmacokinetics of fosfomycin comparing SOC versus SOC plus fosfomycin. Sixty-one neonates received fosfomycin (100 mg/kg IV q12h for 48 h) and then they converted to oral therapy at the same dose. Two plasma pharmacokinetic samples were taken following the first IV and oral doses, sample times were randomized to cover the whole pharmacokinetic profile and opportunistic CSF pharmacokinetic samples were collected. A population pharmacokinetic model was developed in NONMEM and simulations were performed.

Results: In total, 238 plasma and 15 CSF concentrations were collected. A two-compartment disposition model, with an additional CSF compartment and first-order absorption, best described the data. Bioavailability was estimated as 0.48 (95% CI = 0.347-0.775) and the CSF/plasma ratio as 0.32 (95% CI = 0.272-0.409). Allometric weight and postmenstrual age (PMA) scaling was applied; additional covariates included postnatal age (PNA) on clearance and CSF protein on CSF/plasma ratio.

Conclusions: Through this analysis a population pharmacokinetic model has been developed that can be used alongside currently available pharmacodynamic targets to select a neonatal fosfomycin dose based on an infant's PMA, PNA and weight.

Antimicrob Agents Chemother. 2021 Jun 17;65(7):e0029321.
doi: 10.1128/AAC.00293-21. Epub 2021 Jun 17.

Amikacin Combined with Fosfomycin for Treatment of Neonatal Sepsis in the Setting of Highly Prevalent Antimicrobial Resistance

Christopher A Darlow[1], Fernando Docobo-Perez[2], Nicola Farrington[1], Adam Johnson[1], Laura McEntee[1], Jennifer Unsworth[1], Ana Jimenez-Valverde[1], Silke Gastine[3], Ruwanthi Kolamunnage-Dona[4], Renata M A de Costa[5], Sally Ellis[5], François Franceschi[5], Joseph F Standing[3], Mike Sharland[6], Michael Neely[7], Laura Piddock[5,8], Shampa Das[1], William Hope[1]

Abstract

Antimicrobial resistance (particularly through extended-spectrum β-lactamase and aminoglycoside-modifying enzyme production) in neonatal sepsis is a global problem, particularly in low- and middle-income countries, with significant mortality rates. High rates of resistance are reported for the current WHO-recommended first-line antibiotic regimen for neonatal sepsis, i.e., ampicillin and gentamicin. We assessed the utility of fosfomycin and amikacin as a potential alternative regimen to be used in settings of increasingly prevalent antimicrobial resistance. The combination was studied in a 16-arm dose-ranged hollow-fiber infection model (HFIM) experiment. The combination of amikacin and fosfomycin enhanced bactericidal activity and prevented the emergence of resistance, compared to monotherapy with either antibiotic. Modeling of the experimental quantitative outputs and data from checkerboard assays indicated synergy. We further assessed the combination regimen at clinically relevant doses in the HFIM with nine *Enterobacterales* strains with high fosfomycin and amikacin MICs and demonstrated successful kill to sterilization for 6/9 strains. From these data, we propose a novel combination breakpoint threshold for microbiological success for this antimicrobial combination against *Enterobacterales* strains, i.e., $MIC_F \times MIC_A < 256$ (where MIC_F and MIC_A are the fosfomycin and amikacin MICs, respectively). Monte Carlo simulations predict that a standard fosfomycin-amikacin neonatal regimen would achieve >99% probability of pharmacodynamic success for strains with MICs below this threshold. We conclude that the combination of fosfomycin with amikacin is a viable regimen for the empirical treatment of neonatal sepsis and is suitable for further clinical assessment in a randomized controlled trial.

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doi: 10.1007/s12098-021-03794-6. Online ahead of print.

Ten Versus 14 Days of Antibiotic Therapy in Culture-Proven Neonatal Sepsis: A Randomized, Controlled Trial

Asha Reddy[1], Veeraraja Sathenahalli[2], Niranjan Shivanna[1], Naveen Benakappa[1], Prathik Bandiya[3]

Abstract

Objectives: To compare the efficacy of 10 d versus 14 d of antibiotic therapy in neonates with culture-positive sepsis.

Methods: Neonates with culture-positive sepsis were randomized to either 10-d or 14-d antibiotic therapy. These neonates were followed up to 28 d after discharge for treatment failure. Primary outcome of the study was treatment failure which was defined as readmission to the NICU within 4 wk of discharge with blood culture growing same organism with similar antibiogram or any readmission with signs of sepsis with negative blood culture.

Results: A total of 70 neonates were randomized to receive either 10 d (n = 35) or 14 d (n = 35) of antibiotic therapy. Gram-negative infections were encountered in majority of the neonates. Treatment failure occurred in 1 neonate in 10-d group and none in 14-d group. The

duration of hospital stay was significantly less in 10-d group as compared to 14-d group (16 d vs. 23 d, p < 0.01).
Conclusions: Ten days of antibiotics in neonates with culture-positive sepsis, who have achieved clinical and microbiologic remission at day 7, is noninferior to 14 d of therapy. Larger adequately powered trials will address this issue with certainty.

Trans R Soc Trop Med Hyg. 2020 Aug 1;114(8):566-574.
doi: 10.1093/trstmh/traa023.
Feasibility of manual white blood cell counts as a predictor of neonatal sepsis in a low-resource setting
Christian N Golding[1 2 3], Frederik Schaltz-Buchholzer[1 3 4], Lilica Sanca[1], Clara Clipet-Jensen[3], Christine S Benn[1 3 4], Nicholas Au[5], Kate Chipperfield[5], Tobias R Kollmann[6], Nelly A Amenyogbe[7]
Abstract
Background: Manual white blood cell (WBC) differential counts as a predictor for neonatal sepsis development in a low-resource setting have not been thoroughly evaluated. We hypothesized that manual differentiation (specifically immature:total [I:T] neutrophil ratios) would be feasible and useful as an adjunct to predict early-onset neonatal sepsis (EONS). Secondarily, we hypothesized that vaccination with bacillus Calmette-Guérin (BCG) and oral polio vaccine (OPV) could alter WBC differential counts and thus might reduce its predictive performance.
Methods: We performed a prospective cohort study within a randomized trial, randomizing healthy, high-risk newborns admitted to the nursery at the national hospital in Guinea-Bissau 1:1 to BCG+OPV at admission or at discharge (usual practice). Thin capillary blood films were prepared at 2 d of age in a subset of 268 neonates. WBC counts were assessed by microscopy and neonates were followed up for sepsis development within 2 weeks.
Results: Ninety-eight percent (264/268) of smears provided interpretable reads. Of the 264 children, 136 had been randomized to receive BCG+OPV prior to sampling; the remaining 128 were vaccinated at discharge. The I:T ratio (average 0.017) was lower among children who did not develop clinical sepsis but did not predict sepsis (p=0.70). Only three children had an I:T ratio >0.2 (associated with a higher probability of clinical sepsis in previous studies) but did not develop sepsis. Immunization did not alter WBC composition.
Conclusions: Manual WBC differentials are feasible in low-resource settings. WBC differentials are not affected by standard newborn immunization. However, the I:T ratio had no value in predicting subsequent development of sepsis.

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doi: 10.1007/s12098-020-03412-x. Epub 2020 Jul 9.
Oral versus Injectable Antibiotics in Asymptomatic Neonates Born to Mothers with Risk Factors for Sepsis: A Pilot Randomized Controlled Trial
Ashok Kumar[1], Abhishek Kumar Dubey[2], Sriparna Basu[3]

Abstract
Objective: To compare oral co-amoxiclav with injectable ampicillin and amikacin for the management of asymptomatic neonates born to mothers with risk factors for infection.
Methods: This open label, randomized controlled trial was conducted in a tertiary care teaching hospital on neonates of gestational age ≥ 34 wk with maternal risk factors for infection, who were asymptomatic at birth and accepting breastfeeds. Newborns were randomized to receive either oral co-amoxiclav or injectable ampicillin and amikacin within 1-3 h after birth. Primary outcome variable was the development of clinical signs of sepsis with or without a positive blood culture by 72 h of life. Secondary outcome variables were development of sepsis with or without a positive blood culture by 7 d of life and adverse effects of drug therapy.
Results: One hundred twenty-six newborns were randomized to receive either oral co-amoxyclav (n = 63) or injectable ampicillin and amikacin (n = 63). Data were analyzed on intention to treat basis. Both groups were comparable with respect to maternal and neonatal characteristics. Incidence of clinical sepsis within three days of age was similar between the groups [2 (3.2%) vs. 1 (1.6%) in injectable and oral groups, respectively; RR (95% CI) 0.500 (0.047-5.373); p = 0.567]. No significant difference was noted for the development of sepsis by 1 wk [1 (1.6%) vs. 0 in injectable and oral groups, respectively; RR (95% CI) 0.333 (0.014-8.03100); p = 0.499]. Adverse drug reactions such as vomiting, diarrhea and skin rash were infrequent and comparable in two groups.
Conclusions: Oral co-amoxyclav is as effective as injectable ampicillin and amikacin for management of asymptomatic neonates born to mothers with risk factors for infection.

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doi: 10.1002/14651858.CD001150.pub4.

Topical emollient for preventing infection in preterm infants

Jemma Cleminson[1], William McGuire[1]

Abstract
Background: Breakdown of the developmentally immature epidermal barrier may permit entry for micro-organisms leading to invasive infection in preterm infants. Topical emollients may improve skin integrity and barrier function and thereby prevent invasive infection, a major cause of mortality and morbidity in preterm infants.
Objectives: To assess the effect of topical application of emollients (ointments, creams, or oils) on the risk of invasive infection and mortality in preterm infants.
Search methods: We searched CENTRAL via Cochrane Register of Studies (CRS) Web and MEDLINE via Ovid (updated 08 January 2021) and the reference lists of retrieved articles.
Selection criteria: Randomised or quasi-randomised controlled trials that assessed the effect of prophylactic application of topical emollient on the risk of invasive infection, mortality, other morbidity, and growth and development in preterm infants.
Data collection and analysis: We used the standard methods of Cochrane Neonatal. Two review authors separately evaluated trial quality, extracted data, and synthesised effect estimates using risk ratio (RR), risk difference (RD), and mean difference. We used the GRADE approach to assess the certainty of evidence for effects on mortality and invasive infection.
Main results: We included 22 trials with a total of 5578 infant participants. The main potential sources of bias were lack of clarity on the methods used to generate random sequences and conceal allocation in half of the trials, and lack of masking of parents,

caregivers, clinicians, and investigators in all of the trials. Eight trials (2086 infants) examined the effect of topical ointments or creams. Most participants were very preterm infants cared for in healthcare facilities in high-income countries. Meta-analyses suggested that topical ointments or creams may have little or no effect on invasive infection (RR 1.13, 95% confidence interval (CI) 0.97 to 1.31; low certainty evidence) or mortality (RR 0.94, 95% CI 0.82 to 1.08; low certainty evidence). Fifteen trials (3492 infants) assessed the effect of topical plant or vegetable oils. Most of these trials were undertaken in low- or middle-income countries and were based in healthcare facilities. One large (2249 infants) community-based trial occurred in a rural field practice in India. Meta-analyses suggested that topical oils may reduce invasive infection (RR 0.71, 95% CI 0.52 to 0.96; I^2 = 52%; low certainty evidence) but have little or no effect on mortality (RR 0.94, 95% CI 0.82 to 1.08, I^2 = 3%; low certainty evidence). One trial (316 infants) that compared petroleum-based ointment versus sunflower seed oil in very preterm infants in Bangladesh showed little or no effect on invasive infection (RR 0.91, 95% CI 0.57 to 1.46; low certainty evidence), but suggested that ointment may lower mortality slightly (RR 0.82, 95% CI 0.68 to 0.98; RD -0.12, 95% CI -0.23 to -0.01; number needed to treat for an additional beneficial outcome 8, 95% CI 4 to 100; low certainty evidence). One trial (64 infants) that assessed the effect of coconut oil versus mineral oil in preterm infants with birth weight 1500 g to 2000 g in India reported no episodes of invasive infection or death in either group (very low certainty evidence).
Authors' conclusions: The level of certainty about the effects of emollient therapy on invasive infection or death in preterm infants is low. Since these interventions are mostly inexpensive, readily accessible, and generally acceptable, further good-quality randomised controlled trials in healthcare facilities, and in community settings in low- or middle-income countries, may be justified.

Am J Clin Nutr. 2020 Jul 1;112(1):106-112.
doi: 10.1093/ajcn/nqaa102.

Human milk oligosaccharides and their association with late-onset neonatal sepsis in Peruvian very-low-birth-weight infants

Victor D Torres Roldan[1], Meritxell Urtecho S[1], Julia Gupta[2], Chloe Yonemitsu[2], Cesar P Cárcamo[3], Lars Bode[2], Theresa J Ochoa[1,4,5]

Abstract
Background: Oligosaccharides are the third most abundant component in human milk. They are a potential protective agent against neonatal sepsis.
Objectives: We aimed to explore the association between human milk oligosaccharides (HMOs) and late-onset sepsis in very-low-birth-weight infants, and to describe the composition and characteristics of HMOs in Peruvian mothers of these infants.
Methods: This is a secondary data analysis of a randomized clinical trial. We conducted a retrospective cohort study of mothers and their very-low-birth-weight (<1500 g) infants with ≥1 milk sample and follow-up data for >30 d. HMOs were measured by high performance liquid chromatography (HPLC). We used factor analysis and the Mantel-Cox test to explore the association between HMOs and late-onset neonatal sepsis.
Results: We included 153 mother-infant pairs and 208 milk samples. Overall, the frequency of the secretor phenotype was 93%. Secretors and nonsecretors were defined by the presence and near-absence of α1-2-fucosylated HMOs, respectively. The most abundant

oligosaccharides were 2'-fucosyllactose, lacto-N-fucopentaose (LNFP) I, and difucosyllacto-N-tetraose in secretors and lacto-N-tetraose and LNFP II in nonsecretors. Secretors had higher amounts of total oligosaccharides than nonsecretors (11.45 g/L; IQR: 0.773 g/L compared with 8.04 g/L; IQR: 0.449 g/L). Mature milk samples were more diverse in terms of HMOs than colostrum (Simpson's Reciprocal Diversity Index). We found an association of factor 3 in colostrum with a reduced risk of late-onset sepsis (HR: 0.63; 95% CI: 0.41, 0.97). Fucosyl-disialyllacto-N-hexose (FDSLNH) was the only oligosaccharide correlated to factor 3. **Conclusions:** These findings suggest that concentrations of different HMOs vary from one individual to another according to their lactation period and secretor status. We also found that FDSLNH might protect infants with very low birth weight from late-onset neonatal sepsis. Confirming this association could prove 1 more mechanism by which human milk protects infants against infections and open the door to clinical applications of HMOs

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Aqueous chlorhexidine 1% versus 2% for neonatal skin antisepsis: a randomised non-inferiority trial

Akash Sharma[1], Srikant Kulkarni[1], Anu Thukral[1], M Jeeva Sankar[1], Ramesh Agarwal[2], A K Deorari[1], Sarita Mohapatra[3], Thirumurthy Velpandian[4], Minu Bajpai[5]

Abstract

Objective: To evaluate whether 1% aqueous chlorhexidine gluconate (CHG) when compared with 2% aqueous chlorhexidine gluconate is non-inferior for neonatal skin antisepsis.

Design: Parallel, blinded, non-inferiority randomised trial.

Setting: Level III, academic, neonatal intensive care unit.

Patients: Infants born at $26^{0/7}$ to $42^{6/7}$ weeks of gestation from June 2019 to December 2019.

Interventions: Participants were randomised to skin antisepsis by either 1% aqueous CHG or 2% aqueous CHG.

Main outcome measures: The primary outcome was the proportion of negative skin swab cultures after skin antisepsis. Secondary outcomes were local skin reactions at 0, 6, 12 and 24 hours and plasma chlorhexidine levels in a subset of the study population.

Results: A total of 308 neonates with a median gestation age of 34 (31-37) weeks and mean birth weight of 2029 g were randomised on 685 occasions (1% CHG: n=341; 2% CHG: n=344). 93.0% of the post-antisepsis skin swabs were sterile in 1% CHG group compared with 95.6% of the swabs in the 2% CHG group (risk difference -2.7%, 95% CI -6.2% to +0.8%). The lower bound of 95% CI crossed the pre-specified absolute non-inferiority limit of 5%. Neonates developed mild dermatitis on 16 (2.3%) occasions. There was no significant difference in median plasma CHG levels in the two groups, 19.6 (12.5-36.4) and 12.6 (8.7-26.6) ng/mL, respectively.

Conclusions: Application of 1% aqueous CHG was not shown to be non-inferior to 2% chlorhexidine aqueous for skin antisepsis in neonates. There were no severe skin-related adverse events in either of the two groups.

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Hand hygiene for the prevention of infections in neonates

Bankole Peter Kuti[1], Tinuade A Ogunlesi[2], Olabisi Oduwole[3], Chukwudi Oringanje[4], Ekong E Udoh[5], Martin M Meremikwu[6]

Abstract

Background: Annually, infections contribute to approximately 25% of the 2.8 million neonatal deaths worldwide. Over 95% of sepsis-related neonatal deaths occur in low- and middle-income countries. Hand hygiene is an inexpensive and cost-effective method of preventing infection in neonates, making it an affordable and practicable intervention in low- and middle-income settings. Therefore, hand hygiene practices may hold strong prospects for reducing the occurrence of infection and infection-related neonatal death.

Objectives: To determine the effectiveness of different hand hygiene agents for preventing neonatal infection in community and health facility settings.

Search methods: We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 5), in the Cochrane Library; MEDLINE via PubMed (1966 to 10 May 2019); Embase (1980 to 10 May 2019); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 10 May 2019). We also searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-randomised trials. Searches were updated 1 June 2020.

Selection criteria: We included RCTs, cross-over trials, and quasi-RCTs that included pregnant women, mothers, other caregivers, and healthcare workers who received interventions within the community or in health facility settings DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane and the GRADE approach to assess the certainty of evidence. Primary outcomes were incidence of (study author-defined) suspected infection within the first 28 days of life, bacteriologically confirmed infection within the first 28 days of life, all-cause mortality within the first seven days of life (early neonatal death), and all-cause mortality from the 8th to the 28th day of life (late neonatal death).

Main results: Our review included five studies: one RCT, one quasi-RCT, and three cross-over trials with a total of more than 5450 neonates (two studies included all neonates but did not report the actual number of neonates involved). Four studies involved 279 nurses working in neonatal intensive care units and all neonates on admission. The fifth study did not clearly state how many nurses were included in the study. Studies examined the effectiveness of different hand hygiene practices for the incidence of (study author-defined) suspected infection within the first 28 days of life. Two studies were rated as low risk for selection bias, another two were rated as high risk, and one study was rated as unclear risk. One study was rated as low risk for allocation bias, and four were rated as high risk. Only one of the five studies was rated as low risk for performance bias. 4% chlorhexidine gluconate (CHG) compared to plain liquid soap We are uncertain whether plain soap is better than 4% chlorhexidine gluconate (CHG) for nurses' skin based on very low-certainty evidence (mean difference (MD) -1.75, 95% confidence interval (CI) -3.31 to -0.19; 16 participants, 1 study; very low-certainty evidence). We identified no studies that reported on other outcomes for this comparison. 4% chlorhexidine gluconate compared to triclosan 1% One study compared 1% w/v triclosan with 4% chlorhexidine gluconate and suggests that 1% w/v triclosan may reduce the incidence of suspected infection (risk ratio (RR) 1.04, 95% CI 0.19 to 5.60; 1916

participants, 1 study; very low-certainty evidence). There may be fewer cases of infection in the 1% w/v triclosan group compared to the 4% chlorhexidine gluconate group (RR 6.01, 95% CI 3.56 to 10.14; 1916 participants, 1 study; very low-certainty evidence); however, we are uncertain of the available evidence. We identified no study that reported on all-cause mortality, duration of hospital stay, and adverse events for this comparison. 2% CHG compared to alcohol hand sanitiser (61% alcohol and emollients) We are uncertain whether 2% chlorhexidine gluconate reduces the risk of all infection in neonates compared to 61% alcohol hand sanitiser with regards to the incidence of all bacteriologically confirmed infection within the first 28 days of life (RR 2.19, 95% CI 1.79 to 2.69; 2932 participants, 1 study; very low-certainty evidence) in the 2% chlorhexidine gluconate group, but the evidence is very uncertain. The adverse outcome was reported as mean visual scoring on the skin. There may be little to no difference between the effects of 2% CHG on nurses' skin compared to alcohol hand sanitiser based on very low-certainty evidence (MD 0.80, 95% CI 0.01 to 1.59; 118 participants, 1 study; very low-certainty evidence). We identified no study that reported on all-cause mortality and other outcomes for this comparison. None of the included studies assessed all-cause mortality within the first seven days of life nor duration of hospital stay. AUTHORS' CONCLUSIONS: We are uncertain as to the superiority of one hand hygiene agent over another because this review included very few studies with very serious study limitations.

Jaundice

Eur J Pediatr. 2021 Mar;180(3):767-773.
doi: 10.1007/s00431-020-03763-9. Epub 2020 Aug 19.
Chest shielding in preterm neonates under phototherapy-a randomised control trial
Saurabh Kapoor[1234], Divya Mishra[1234], Deepak Chawla[1234], Suksham Jain[5678]
Abstract
Shielding the precordium can effect manifestation of haemodynamically significant patent ductus arteriosus (hsPDA). Preterm neonates born at ≤ 32 weeks of gestation if needed phototherapy within 72 h of birth and had no echocardiographically proven hsPDA were eligible to be enrolled in this open-label randomised controlled trial. In chest shielding group, in addition to the standard care, left side of the chest was covered using food grade aluminium foil during phototherapy while control group received standard care. Mean gestational age (weeks; 30.1 ± 1.5 vs 30.1 ± 1.6) was comparable in the two groups. However, neonates in the chest shield group had lower birth weight (g; 1281 ± 259 vs 1422 ± 307) and were more likely to be small-for-gestational age (21.6% vs 8.0%). It was seen that 4 (7.8%) babies in the chest shield group and 5 (10%) babies in the standard group developed hsPDA after starting phototherapy with relative risk (RR) of 0.78 (95% CI 0.22-2.75). The left atrium to aortic ratio was significantly different in the two groups with 1.5 ± 0.1 in the chest shield group and 1.8 ± 0.2 in standard group (p value 0.03).Conclusion: Chest shielding of preterm babies during phototherapy has no effect on the incidence of haemodynamically significant patent ductus arteriosus.

Nutrition

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Growth monitoring

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Observed feeding behaviours and effects on child weight and length at 12 months of age: Findings from the SPRING cluster-randomized controlled trial in rural India

Pauline Boucheron[1], Sunil Bhopal[1], Deepali Verma[2], Reetabrata Roy[1,2], Divya Kumar[2], Gauri Divan[2], Betty Kirkwood[1]

Abstract

Background: Child undernutrition results in poor growth in early childhood, undermines optimal development and increases the risk of mortality. Responsive feeding has been promoted as a key intervention for improving nutritional status, however measurement of this remains difficult and has rarely considered child behaviour. We therefore developed a new observed feeding tool to assess both child and caregiver behaviours, as well as their interaction during feeding, and investigate the effect of these on children anthropometric measures at 12-months of age in rural India.

Methods: Our study was nested within the SPRING cluster-randomized controlled trial in Rewari, North India. Outcomes were children length-for-age (LAZ), weight-for-length (WLZ) and weight-for-age (WAZ) Z scores at 12 months of age, based on the WHO Child Growth standards. Trained non-specialists live-coded feeding episodes using the newly designed tool. Scores were then created using principal components analysis representing child behaviour, caregiver behaviour and caregiver-child interaction. Mixed effects linear regression was used to assess associations between feeding behaviours and anthropometric outcomes.

Results: 857 children had a meal observation and were included. Anthropometric status was poor (mean length-for-age -1.59 (SD = 1.11); mean weight-for-length -0.58 (0.95); mean weight-for-age -1.22 (1.04)). There were positive linear differences in weight-for-length per unit increase in caregiver responsive behaviours score (adjusted β-coeff = 0.006, 95%CI = (0.001, 0.011), p = 0.01), in length-for-age and weight-for-age per unit increase in child responsive behaviours score (respectively adjusted β-coeff = 0.004, 95%CI = (0.001, 0.007), p = 0.02, and adjusted β-coeff = 0.003, 95%CI = (0.00001, 0.006), p = 0.049), and in both weight-for-length and weight-for-age per unit increase in caregiver-child interaction score (respectively adjusted β-coeff = 0.007, 95%CI = (0.003, 0.012), p = 0.001, and adjusted β-coeff = 0.005, 95%CI = (0.001, 0.011), p = 0.01). No association was seen between child behaviours and weight-for-length, caregiver behaviours and length and caregiver-child interaction and length.

Conclusions: We found that trained non-specialists could assess feeding episodes using a newly designed checklist. Further, child and caregiver behaviours were associated with weight and length at only 12 months of age, a reminder of the importance of interventions to

improve responsive feeding quality as we strive towards achievement of the sustainable development goals.

Micronutients, multivitamins, and food fortification

(See also Vitamin A)

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A Randomized Multiple Micronutrient Powder Point-of-Use Fortification Trial Implemented in Indian Preschools Increases Expressive Language and Reduces Anemia and Iron Deficiency

Maureen M Black[1,2], Sylvia Fernandez-Rao[3], Krishnapillai Madhavan Nair[4], Nagalla Balakrishna[5], Nicholas Tilton[6], Kankipati Vijaya Radhakrishna[7], Punjal Ravinder[4], Kimberly B Harding[8], Gregory Reinhart[9], Doris P Yimgang[6], Kristen M Hurley[10]

Abstract

Background: Anemia is a global public health problem that undermines childhood development. India provides government-sponsored integrated nutrition/child development preschools.

Objectives: This double-masked, cluster-randomized controlled trial examines whether point-of-use multiple micronutrient powder (MNP) compared with placebo fortification of preschool meals impacts child development and whether effects vary by preschool quality (primary outcome) and biomarkers of anemia and micronutrients (secondary outcomes). We also measured growth and morbidity.

Methods: We randomly assigned 22 preschools in rural India to receive MNP/placebo fortification. We administered baseline and endline blood sampling and measures of childhood development (Mullen Scales of Early Learning, inhibitory control, social-emotional), anthropometry, and morbidity to preschoolers (aged 29-49 mo). Preschools added MNP/placebo to meals 6 d/wk for 8 mo. We conducted linear mixed-effects regression models accounting for preschool clustering and repeated measures. We evaluated child development, examining effects in high- compared with low-quality preschools using the Early Childhood Environment Rating Scale-Revised and the Home Observation for the Measurement of the Environment Inventory, modified for preschools.

Results: At baseline, mean age ± SD was 36.6 ± 5.7 mo, with 47.8% anemic, 41.9% stunted, and 20.0% wasted. Baseline expressive/receptive language scores were higher in high-quality compared with low-quality preschools (P = 0.02 and P = 0.03, respectively). At endline (91% retention, n = 293/321), we found MNP compared with placebo effects in expressive language (Cohen's standardized effect d = 0.4), inhibitory control (d = 0.2), and social-emotional (d = 0.3) in low-quality, not high-quality, preschools. MNP had significantly greater reduction of anemia and iron deficiency compared with placebo (37% compared with 13.5% and 41% compared with 1.2%, respectively). There were no effects on growth or morbidity.

Conclusions: Providing multiple micronutrient-fortified meals in government-sponsored preschools is feasible; reduced anemia and iron deficiency; and, in low-quality preschools, increased preschoolers' expressive language and inhibitory control and reduced developmental disparities. Improving overall preschool quality by incorporating multiple

components of nurturing care (responsive care, learning, and nutrition) may be necessary to enhance preschoolers' development. This trial was registered at clinicaltrials.gov as NCT01660958.

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Effects of vitamin B12 supplementation on neurodevelopment and growth in Nepalese Infants: A randomized controlled trial

Tor A Strand[1,2], Manjeswori Ulak[2,3], Mari Hysing[4], Suman Ranjitkar[3], Ingrid Kvestad[5], Merina Shrestha[3], Per M Ueland[6], Adrian McCann[6], Prakash S Shrestha[3], Laxman S Shrestha[3], Ram K Chandyo[7]

Abstract

Background: Vitamin B12 deficiency is common and affects cell division and differentiation, erythropoiesis, and the central nervous system. Several observational studies have demonstrated associations between biomarkers of vitamin B12 status with growth, neurodevelopment, and anemia. The objective of this study was to measure the effects of daily supplementation of vitamin B12 for 1 year on neurodevelopment, growth, and hemoglobin concentration in infants at risk of deficiency.

Methods and findings: This is a community-based, individually randomized, double-blind placebo-controlled trial conducted in low- to middle-income neighborhoods in Bhaktapur, Nepal. We enrolled 600 marginally stunted, 6- to 11-month-old infants between April 2015 and February 2017. Children were randomized in a 1:1 ratio to 2 μg of vitamin B12, corresponding to approximately 2 to 3 recommended daily allowances (RDAs) or a placebo daily for 12 months. Both groups were also given 15 other vitamins and minerals at around 1 RDA. The primary outcomes were neurodevelopment measured by the Bayley Scales of Infant and Toddler Development 3rd ed. (Bayley-III), attained growth, and hemoglobin concentration. Secondary outcomes included the metabolic response measured by plasma total homocysteine (tHcy) and methylmalonic acid (MMA). A total of 16 children (2.7%) in the vitamin B12 group and 10 children (1.7%) in the placebo group were lost to follow-up. Of note, 94% of the scheduled daily doses of vitamin B12 or placebo were reported to have been consumed (in part or completely). In this study, we observed that there were no effects of the intervention on the Bayley-III scores, growth, or hemoglobin concentration. Children in both groups grew on an average 12.5 cm (SD: 1.8), and the mean difference was 0.20 cm (95% confidence interval (CI): -0.23 to 0.63, P = 0.354). Furthermore, at the end of the study, the mean difference in hemoglobin concentration was 0.02 g/dL (95% CI: -1.33 to 1.37, P = 0.978), and the difference in the cognitive scaled scores was 0.16 (95% CI: -0.54 to 0.87, P = 0.648). The tHcy and MMA concentrations were 23% (95% CI: 17 to 30, P < 0.001) and 30% (95% CI: 15 to 46, P < 0.001) higher in the placebo group than in the vitamin B12 group, respectively. We observed 43 adverse events in 36 children, and these events were not associated with the intervention. In addition, 20 in the vitamin B12 group and 16 in the placebo group were hospitalized during the supplementation period. Important limitations of the study are that the strict inclusion criteria could limit the external validity and that the period of vitamin B12 supplementation might not have covered a critical window for infant growth or brain development.

Conclusions: In this study, we observed that vitamin B12 supplementation in young children at risk of vitamin B12 deficiency resulted in an improved metabolic response but did not affect neurodevelopment, growth, or hemoglobin concentration. Our results do not support widespread vitamin B12 supplementation in marginalized infants from low-income countries.

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Wheat flour fortification with iron and other micronutrients for reducing anaemia and improving iron status in populations

Martha S Field[1], Prasanna Mithra[2], Juan Pablo Peña-Rosas[3]

Abstract

Background: Anaemia is a condition where the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiological needs. Fortification of wheat flour is deemed a useful strategy to reduce anaemia in populations.

Objectives: To determine the benefits and harms of wheat flour fortification with iron alone or with other vitamins and minerals on anaemia, iron status and health-related outcomes in populations over two years of age.

Search methods: We searched CENTRAL, MEDLINE, Embase, CINAHL, 21 other databases and two trials registers up to 21 July 2020, together with contacting key organisations to identify additional studies.

Selection criteria: We included cluster- or individually-randomised controlled trials (RCTs) carried out among the general population from any country, aged two years and above. The interventions were fortification of wheat flour with iron alone or in combination with other micronutrients. We included trials comparing any type of food item prepared from flour fortified with iron of any variety of wheat DATA COLLECTION AND ANALYSIS: Two review authors independently screened the search results and assessed the eligibility of studies for inclusion, extracted data from included studies and assessed risks of bias. We followed Cochrane methods in this review.

Main results: Our search identified 3538 records, after removing duplicates. We included 10 trials, involving 3319 participants, carried out in Bangladesh, Brazil, India, Kuwait, Philippines, South Africa and Sri Lanka. We identified two ongoing studies and one study is awaiting classification. The duration of interventions varied from 3 to 24 months. One study was carried out among adult women and one trial among both children and nonpregnant women. Most of the included trials were assessed as low or unclear risk of bias for key elements of selection, performance or reporting bias. Three trials used 41 mg to 60 mg iron/kg flour, three trials used less than 40 mg iron/kg and three trials used more than 60 mg iron/kg flour. One trial used various iron levels based on type of iron used: 80 mg/kg for electrolytic and reduced iron and 40 mg/kg for ferrous fumarate. All included studies contributed data for the meta-analyses. Iron-fortified wheat flour with or without other micronutrients added versus wheat flour (no added iron) with the same other micronutrients added Iron-fortified wheat flour with or without other micronutrients added versus wheat flour (no added iron) with the same other micronutrients added may reduce by 27% the risk of anaemia in populations (risk ratio (RR) 0.73, 95% confidence interval (CI) 0.55 to 0.97; 5

studies, 2315 participants; low-certainty evidence). It is uncertain whether iron-fortified wheat flour with or without other micronutrients reduces iron deficiency (RR 0.46, 95% CI 0.20 to 1.04; 3 studies, 748 participants; very low-certainty evidence) or increases haemoglobin concentrations (in g/L) (mean difference MD 2.75, 95% CI 0.71 to 4.80; 8 studies, 2831 participants; very low-certainty evidence). No trials reported data on adverse effects in children (including constipation, nausea, vomiting, heartburn or diarrhoea), except for risk of infection or inflammation at the individual level. The intervention probably makes little or no difference to the risk of Infection or inflammation at individual level as measured by C-reactive protein (CRP) (mean difference (MD) 0.04, 95% CI -0.02 to 0.11; 2 studies, 558 participants; moderate-certainty evidence). Iron-fortified wheat flour with other micronutrients added versus unfortified wheat flour (nil micronutrients added) It is unclear whether wheat flour fortified with iron, in combination with other micronutrients decreases anaemia (RR 0.77, 95% CI 0.41 to 1.46; 2 studies, 317 participants; very low-certainty evidence). The intervention probably reduces the risk of iron deficiency (RR 0.73, 95% CI 0.54 to 0.99; 3 studies, 382 participants; moderate-certainty evidence) and it is unclear whether it increases average haemoglobin concentrations (MD 2.53, 95% CI -0.39 to 5.45; 4 studies, 532 participants; very low-certainty evidence). No trials reported data on adverse effects in children. Nine out of 10 trials reported sources of funding, with most having multiple sources. Funding source does not appear to have distorted the results in any of the assessed trials.

Authors' conclusions: Fortification of wheat flour with iron (in comparison to unfortified flour, or where both groups received the same other micronutrients) may reduce anaemia in the general population above two years of age, but its effects on other outcomes are uncertain. Iron-fortified wheat flour in combination with other micronutrients, in comparison with unfortified flour, probably reduces iron deficiency, but its effects on other outcomes are uncertain. None of the included trials reported data on adverse side effects except for risk of infection or inflammation at the individual level. The effects of this intervention on other health outcomes are unclear. Future studies at low risk of bias should aim to measure all important outcomes, and to further investigate which variants of fortification, including the role of other micronutrients as well as types of iron fortification, are more effective, and for whom.

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The association of urine markers of iodine intake with development and growth among children in rural Uganda: a secondary analysis of a randomised education trial

Prudence Atukunda[1], Grace Km Muhoozi[1 2], Lien M Diep[3], Jens P Berg[4 5], Ane C Westerberg[6], Per O Iversen[1 7 8]

Abstract

Objective: We examined associations of urine iodide excretion, proxy for iodine intake, with child development and growth.

Design: This is a secondary analysis of a 1:1 cluster-randomised trial with a 6-month nutrition/stimulation/hygiene education intervention among mothers of children aged 6-8 months to improve child development and growth. Development was assessed using Bayley

Scales of Infant and Toddler Development-III (BSID-III) and Ages and Stages Questionnaire (ASQ), whereas anthropometry was used to assess growth. Urine iodide concentration (UIC) and urine iodide/creatinine ratio (ICR) were measured.
Setting: The current study was conducted in southern Uganda.
Participants: We randomly selected 155 children from the 511 enrolled into the original trial and analysed data when they were aged 20-24 and 36 months.
Results: Median UIC for both study groups at 20-24 and 36 months were similar (P > 0·05) and within the normal range of 100-199 µg/l (0·79-1·60 µmol/l), whereas the intervention group had significantly higher ICR at 20-24 months. The BSID-III cognitive score was positively associated (P = 0·028) with ICR at 20-24 months in the intervention group. The ASQ gross motor score was negatively associated (P = 0·020) with ICR at 20-24 months among the controls. ICR was not significantly associated with anthropometry in the two study groups at either time-point.
Conclusions: Following the intervention, a positive association was noted between ICR and child's cognitive score at 20-24 months, whereas no positive association with ICR and growth was detected. Iodine sufficiency may be important for child's cognitive development in this setting.

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Effectiveness of various methods of home fortification in under-5 children: where they work, where they do not. A systematic review and meta-analysis
Bahareh Nikooyeh[1], Tirang R Neyestani[1]
Abstract
Context: The common approaches of home fortification (HF) for prevention and/or treatment of micronutrient deficiencies are micronutrient powders (MNPs), foodlets, and lipid-based nutrient supplements (LNSs). There are mixed results for the impact of HF on growth and nutritional status of young children.
Objective: This systematic review was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to evaluate current evidence from randomized controlled trials including children younger than 5 years to assess the effect of strategies of HF on growth and micronutrient status.
Methods: The MEDLINE, PubMed, Embase, Cochrane Library, and Google Scholar databases were searched to July 2018. A total of 1301 studies were found in a preliminary search. After screening of titles and abstracts, 30 studies were selected.
Results: Treatment with MNPs, foodlets, and LNSs effectively increased hemoglobin concentrations by at least 2.52 g/L, 4.59 g/L, and 4.4 g/dL, respectively, as compared with a control. There was a significant decrease in risk of anemia development after foodlet intervention compared with a control or iron drops (odds ratio, 0.27; 95%CI, 0.10-0.74; P = 0.01). However, these interventions did not result in any significant improvement in z-scores for changes of height for age, weight for age, and weight for height. The results indicated that MNP (7.16; 95%CI, 0.31-14.01; P = 0.04) and foodlet treatment (4.92; 95%CI, 0.28-9.57; P = 0.04) could increase serum zinc levels. However, none of the home fortification methods improved vitamin A status in the target group.

Conclusion: Home fortification can be used as an effective method to improve hemoglobin, iron, and zinc status, although in this study it had no effect on vitamin A or anthropometric indicators of the target population. More investigations are warranted for newer approaches of HF to improve a broader range of micronutrients as well as child growth indices and for evaluation of the coverage, compliance, and consistency of such interventions at the population level.

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doi: 10.1136/bmjgh-2020-002705.

Behavioural insights to support increased consumption of quality protein maize by young children: a cluster randomised trial in Ethiopia

Katherine Donato[1], Margaret McConnell[2], Dan Han[3], Nilupa S Gunaratna[4], Masresha Tessema[5], Hugo De Groote[6], Jessica Cohen[7]

Abstract

Introduction: Biofortified crops have tremendous potential to improve child nutrition. We tested whether complementing the distribution of quality protein maize (QPM) with a package of interventions informed by behavioural insights could support greater consumption of QPM by young children and translate into improved growth.

Methods: We conducted a cluster-randomised trial in Oromia, Ethiopia. Clusters of households with a child between 6 and 35 months were randomised into an arm receiving QPM seed only (320 households, 203 clusters) or an arm receiving QPM seed and a child consumption targeting intervention (290 households, 183 clusters). The intervention package included tools to help caregivers keep QPM separate from conventional maize and to earmark QPM specifically for child consumption, as well as encouragement regarding cooking QPM specifically for young children. We analysed the impact of the intervention on food storage, cooking and consumption behaviours and on anthropometric measures (weight-for-age, height-for-age z scores).

Results: The consumption targeting intervention increased the probability of child consumption of QPM in the past week by 17.3 percentage points (pp) (95% CI 9.4 pp to 25.1 pp; p<0.01), increased the probability that QPM flour was stored separately from conventional maize by 46.5 pp (95% CI 38.3 pp to 54.7 pp; p<0.01) and increased the probability that caregivers cooked QPM specifically for young children in the past week by 14.4 pp (95% CI 7.9 pp to 20.9 pp; p<0.01). These effects persisted, but were attenuated, 10 months postintervention. No significant effects on anthropometric outcomes were found.

Conclusions: Enhancing the distribution of new, biofortified crop varieties with a consumption targeting campaign can change storage, cooking and consumption behaviours. However, these improved behaviours did not translate into increased growth in this setting.

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The effect of bovine colostrum/egg supplementation compared with corn/soy flour in young Malawian children: a randomized, controlled clinical trial

Tatiana Bierut[1], Laura Duckworth[1], Mark Grabowsky[2], M Isabel Ordiz[1], Marie L Laury[3], Meghan Callaghan-Gillespie[1], Ken Maleta[4], Mark J Manary[1 4 5]

Abstract

Background: Bovine colostrum with egg powder (BC/egg) is rich in essential amino acids and immunoactive compounds.

Objectives: This trial tested the hypothesis that a daily supplement of BC/egg would reduce linear growth faltering and environmental enteric dysfunction (EED) in Malawian infants when compared with an isoenergetic ration of corn/soy flour used as a control. EED was defined by a lactulose permeability test.

Methods: This was a prospective, randomized, blinded, placebo-controlled clinical trial in which 9-mo-old infants received BC/egg or a control for 3 mo. The primary outcomes were change in length-for-age z-score (ΔLAZ) and urinary lactulose excretion (%L) at 12-mo-old. Secondary outcomes included episodes of diarrhea, stunting, EED, and the 16S configuration of the fecal microbiota.

Results: Of the 277 children enrolled, 267 completed the intervention phase of the study. LAZ decreased in all children from 9 to 17 mo, although ΔLAZ was less in children receiving BC/egg from 9 to 12 mo (difference = 0.12 z-scores; P = 0.0011). This difference persisted after feeding was completed, with less ΔLAZ (difference = 0.09 z-scores). A lower prevalence of stunting was seen in the intervention group (n = 47/137) than the control group (n = 62/127) at 17 mo (RR = 0.70; 95% CI: 0.52, 0.94).The median %L at 12 mo of age in the children receiving BC/egg was 0.14%, compared with 0.17% in the control group (P = 0.74). In children with %L >0.45% at enrollment (severe EED), the BC/egg group had more children with normal %L at 12 mo of age (10/20, 50%) than was seen in controls (2/15, 13%; P = 0.024). Episodes of diarrhea and β-diversity of the 16S configuration of fecal microbiota did not differ between the 2 groups.

Conclusions: Addition of BC/egg to complementary feeding in Malawian infants resulted in less linear growth faltering.

Lipid-based nutrition supplements

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Supplementation with Fortified Lipid-Based and Blended Complementary Foods has Variable Impact on Body Composition Among Rural Bangladeshi Children: A Cluster-Randomized Controlled Trial

Saijuddin Shaikh[1 2], Rebecca K Campbell[2], Sucheta Mehra[2], Alamgir Kabir[3], Kerry J Schulze[2], Lee Wu[2], Hasmot Ali[1 2], Abu Ahmed Shamim[4], Keith P West[2], Parul Christian[2]

Abstract

Background: Complementary food supplementation enhances linear growth and may affect body composition in children.

Objective: We aimed to determine the effect of complementary food supplements provided from the age of 6 to 18 mo on fat-free mass (FFM) and fat mass (FM) gain among children in rural Bangladesh.
Methods: In an unblinded, cluster-randomized, controlled trial we tested the effects of 4 complementary food supplements for 1 y [chickpea, rice lentil, Plumpy'doz, and wheat-soy-blend++ (WSB++)] compared with no supplements on linear growth. Body composition was estimated using weight-length-based, age- and sex-specific equations at 6, 9, 12, 15, and 18 mo and postintervention aged 24 mo. Generalized estimating equations (GEEs) were applied to estimate the effect of each complementary food on mean FFM and FM from 9 to 18 and 24 mo compared with the control, adjusting for baseline measures. Sex interactions were also explored.
Results: In total, 3592 (65.9% of enrolled) children completed all anthropometric assessments. Estimated FFM and FM (mean ± SD) were 5.3 ± 0.6 kg and 1.4 ± 0.4 kg, respectively, at the age of 6 mo. Mean ± SE FFM and FM from 9 to 18 mo were 75.4 ± 14.0 g and 32.9 ± 7.1 g, and 61.0 ± 16.6 g and 30.0 ± 8.4 g, higher with Plumpy'doz and chickpea foods, respectively, than the control ($P < 0.001$). Estimated FFM was 41.5 ± 16.6 g higher in rice-lentil-fed versus control ($P < 0.05$) children. WSB++ had no impact on FFM or FM. A group-sex interaction ($P < 0.1$) was apparent with Plumpy'doz and rice-lentil foods, with girls involved in the intervention having higher estimated FFM and FM than control girls compared with no significant effect in boys. At 24 mo, FFM and FM remained higher only in girls eating Plumpy'doz compared with the controls ($P < 0.01$).
Conclusions: In this randomized trial, supplementation effected small shifts in apparent body composition in rural Bangladeshi children. Where seen, FFM increments were twice that of FM, in proportion to these compartments, and more pronounced in girls. FFM increased in line with reported improvements in length.

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Effect of lipid-based nutrient supplement-Medium quantity on reduction of stunting in children 6-23 months of age in Sindh, Pakistan: A cluster randomized controlled trial

Gul Nawaz Khan[1], Sumra Kureishy[2], Shabina Ariff[1], Arjumand Rizvi[1], Muhammad Sajid[1], Cecilia Garzon[2], Ali Ahmad Khan[2], Saskia de Pee[3 4 5], Sajid Bashir Soofi[1 6], Zulfiqar A Bhutta[1 6]

Abstract
Background: Chronic childhood malnutrition, or stunting, remains a persistent barrier to achieve optimal cognitive development, child growth and ability to reach full potential. Almost half of children under-five years of age are stunted in the province of Sindh, Pakistan.
Objective: The primary objective of this study was to test the hypothesis that the provision of lipid-based nutrient supplement-medium-quantity (LNS-MQ) known as Wawamum will result in a 10% reduction in risk of being stunted at the age of 24 months in the intervention group compared with the control group.
Design: A cluster randomized controlled trial was conducted in Thatta and Sujawal districts of Sindh province, Pakistan. A total of 870 (419 in intervention; 451 in control) children between 6-18 months old were enrolled in the study. The unit of randomization was union

council and considered as a cluster. A total of 12 clusters, 6 in each study group were randomly assigned to intervention and control group. All children received standard government health services, while children in the intervention group also received 50 grams/day of Wawamum.
Results: Children who received Wawamum were found to have a significantly reduced risk of stunting (RR = 0.91, 95% CI; 0.88-0.94, p<0.001) and wasting (RR = 0.78, 95% CI; 0.67-0.92, p = 0.004) as compared to children who received the standard government health services. There was no evidence of a reduction in the risk of underweight (RR = 0.94, 95% CI; 0.85-1.04, p = 0.235) in the intervention group compared to the control group. Statistically significant reduction in anaemia in the intervention group was also found as compared to the control group (RR = 0.97, 95% CI; 0.94-0.99, p = 0.042). The subgroup analysis by age, showed intervention effect is significant in reduction of risk of stunting in younger children of aged 6-12 month (RR = 0.83, 95% CI; 0.81-0.86, p = <0.001) and their older peers aged 13-18 month- (RR = 0.90, 95% CI; 0.83-0.97, p = 0.008). The mean compliance of Wawamum was 60% among children.
Conclusions: The study confirmed that the provision of Wawamum to children 6-23 months of age is effective in reducing the risk of stunting, wasting and anaemia. This approach should be scaled up among the most food insecure areas/households with a high prevalence of stunting to achieve positive outcomes for nutrition and health.

Environmental enteric dysfuction

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Impact of Different Strategies for Delivering Supplemental Zinc on Selected Fecal Markers of Environmental Enteric Dysfunction among Young Laotian Children: A Randomized Controlled Trial
Guy-Marino Hinnouho[1,2], K Ryan Wessells[2], Maxwell A Barffour[3,2], Somphou Sayasone[4], Charles D Arnold[2], Sengchanh Kounnavong[4], Sonja Y Hess[2]
Abstract
The objective of this study was to assess the impact of different strategies for delivering supplemental zinc on fecal myeloperoxidase (MPO), neopterin (NEO), and calprotectin (CAL) among young Laotian children. In a double-blind controlled trial, children aged 6-23 months were randomized to receive either daily preventive zinc (PZ) tablets (7 mg/day), daily micronutrient powder (MNP; containing 10 mg zinc and 14 other micronutrients), therapeutic zinc (TZ) supplements for diarrhea treatment (20 mg/day for 10 days), or daily placebo powder and followed for ~36 weeks. Stool samples were collected at baseline and endline. Fecal MPO, NEO, and CAL concentrations were determined in a randomly selected subsample of 720 children using commercially available ELISA kits. At baseline, the mean age was 14.1 ± 4.9 months and prevalence of stunting was 39%. The endline prevalence of stunting was 43%; there was no overall treatment effect on physical growth in the parent trial. At endline, the mean (95% CI) MPO in the PZ group was 1,590 [1,396; 1,811] ng/mL and

did not differ from that in the MNP (1,633 [1,434; 1,859] ng/mL), TZ (1,749 [1,535; 1,992] ng/mL), and control (1,612 [1,415; 1,836] ng/mL) groups ($P = 0.749$). Similarly, there was no overall treatment effect on NEO and CAL concentrations ($P = 0.226$ and 0.229, respectively). In this population, the provision of PZ or TZ supplements or MNP had no impact on growth or environmental enteric dysfunction (EED) as assessed by fecal MPO, NEO, and CAL. Additional research is needed to better understand the etiology and proposed mechanisms of EED pathogenesis.

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Faecal regenerating 1B protein concentration is not associated with child growth in rural Malawi

Zhifei Liu[1], Yue-Mei Fan[1], Per Ashorn[1,2], Yin Bun Cheung[1,3], Lotta Hallamaa[1], Heikki Hyöty[1,4], Kenneth Maleta[5], Kirsi-Maarit Lehto[1], Sami Oikarinen[1], Seppo Parkkila[1,4], Ulla Ashorn[1]

Abstract

Aim: This study was designed to determine whether faecal regenerating 1B protein (REG1B) concentration is associated with physical growth among 6-30-month-old children in rural Malawi.

Methods: This was a secondary analysis from a randomised controlled trial in rural Malawi in which we followed-up 790 live-born infants from birth to 30 months of age. We collected anthropometric data at the age of 6, 12, 18, 24 and 30 months. We measured faecal REG1B concentration by enzyme-linked immunosorbent assay (ELISA) technique using stool samples collected at 6, 18 and 30 months of age. We assessed the association between faecal REG1B concentration and children's physical growth using linear regression and longitudinal data analysis.

Results: Of 790 live-born infants enrolled, 694 (87%) with at least one faecal REG1B concentration measurement were included in the analysis. Faecal REG1B concentration was not associated with the children's concurrent length-for-age z-score (LAZ), weight-for-age z-score (WAZ), weight-for-length z-score (WLZ) and mid-upper arm circumference-for-age z-score (MUACZ) at any time point ($P > 0.05$), nor with a change in their anthropometric indices in the subsequent 6-month period ($P > 0.05$).

Conclusions: Faecal REG1B concentration is not associated with LAZ, WAZ, WLZ and MUACZ among 6-30-month-old infants and children in rural Malawi.

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Validation of the Micronutrient and Environmental Enteric Dysfunction Assessment Tool and evaluation of biomarker risk factors for growth faltering and vaccine failure in young Malian children

Michael B Arndt[1,2], Jason L Cantera[1], Laina D Mercer[1], Michael Kalnoky[1], Heather N White[1], Gregory Bizilj[1], David S Boyle[1], Eugenio L de Hostos[1], Robert K M Choy[1]

Abstract

Environmental enteric dysfunction (EED) is an intestinal disorder common among children in low-resource settings and is associated with increased risk of growth stunting, cognitive deficits, and reduced oral vaccine immunogenicity. The Micronutrient and EED Assessment Tool (MEEDAT) is a multiplexed immunoassay that measures biomarkers previously associated with child growth faltering and/or oral vaccine immunogenicity: intestinal fatty acid-binding protein (I-FABP), soluble CD14 (sCD14), insulin-like growth factor 1 (IGF-1), and fibroblast growth factor 21 (FGF21). MEEDAT also measures systemic inflammation (α1-acid glycoprotein, C-reactive protein), ferritin, soluble transferrin receptor, retinol binding protein 4, thyroglobulin, and Plasmodium falciparum antigenemia (histidine-rich protein 2). The performance of MEEDAT was compared with commercially available enzyme-linked immunosorbent assays (ELISAs) using 300 specimens from Malian infant clinical trial participants. Regression methods were used to test if MEEDAT biomarkers were associated with seroconversion to meningococcal A conjugate vaccine (MenAV), yellow fever vaccine (YFV), and pentavalent rotavirus vaccine (PRV) after 28 days, or with growth faltering over 12 weeks. The Pearson correlations between the MEEDAT and ELISA results were 0.97, 0.86, 0.80, and 0.97 for serum I-FABP, sCD14, IGF-1, and FGF21, respectively. There were significant associations between I-FABP concentration and the probability of PRV IgG seroconversion and between IGF-1 concentration and the probability of YFV seroconversion. In multivariable models neither association remained significant, however there was a significant negative association between AGP concentration and YFV seroconversion. GLP-2 and sCD14 concentrations were significantly negatively associated with 12-week change in weight-for-age z-score and weight-for-height z-score in multivariable models. MEEDAT performed well in comparison to commercially-available ELISAs for the measurement of four analytes for EED and growth hormone resistance. Adoption of MEEDAT in low-resource settings could help accelerate the identification of interventions that prevent or treat child stunting and interventions that boost the immunogenicity of child vaccinations.

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Gut Bacterial Diversity and Growth among Preschool Children in Burkina Faso

Jean Digitale[1], Ali Sié[2], Boubacar Coulibaly[2], Lucienne Ouermi[2], Clarisse Dah[2], Charlemagne Tapsoba[2], Till Bärnighausen[3 4 5], Elodie Lebas[6], Ahmed M Arzika[7], Medellena Maria Glymour[1], Jeremy D Keenan[8], Thuy Doan[8], Catherine E Oldenburg[8 1]

Abstract

There is a lack of empirical, prospective human data on the gut microbiome and its relationship with growth, especially in low- and middle-income countries. We prospectively assessed the association between gut microbial diversity and short-term growth in a cohort of preschool children in Burkina Faso to better characterize whether there is any evidence that changes in gut microbial diversity may affect growth. Data were obtained from a randomized controlled trial evaluating the effect of antibiotic administration on gut microbial diversity in preschool children. We followed up the enrolled children for 35 days, with anthropometric measurements at baseline and day 35 and microbial diversity measured at baseline and day 9 (analytic sample, *N* = 155). We estimated linear mixed-effects regression models with household random intercepts to assess the association of Simpson's and Shannon's alpha diversity with measures of change in anthropometry (e.g., ponderal

growth since baseline) and absolute anthropometric measurements (e.g., day 35 weight). We did not find evidence that alpha gut microbial diversity was associated with growth or absolute anthropometric measurements after adjusting for confounding variables. Effect estimates were close to the null ($P \geq 0.15$ for all fully adjusted comparisons), with the association between Simpson's alpha diversity and day 35 height (cm) farthest from the null (coefficient = -0.03, 95% CI: -0.07, 0.01). The change in gut microbial diversity also was not associated with the change in anthropometry in crude or adjusted models. Future research is needed to explore whether gut diversity has an impact on growth over a longer time period, in both healthy and malnourished children.

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doi: 10.1038/s41598-020-71922-x.

Infant gut microbiota characteristics generally do not modify effects of lipid-based nutrient supplementation on growth or inflammation: secondary analysis of a randomized controlled trial in Malawi

Riley L Hughes[1], Charles D Arnold[1], Rebecca R Young[1], Per Ashorn[2 3], Ken Maleta[4], Yue-Mei Fan[2], Ulla Ashorn[2], David Chaima[5], Chikondi Malamba-Banda[5], Mary E Kable[6], Kathryn G Dewey[7]

Abstract

An unhealthy gut microbial community may act as a barrier to improvement in growth and health outcomes in response to nutritional interventions. The objective of this analysis was to determine whether the infant microbiota modified the effects of a randomized controlled trial of lipid-based nutrient supplements (LNS) in Malawi on growth and inflammation at 12 and 18 months, respectively. We characterized baseline microbiota composition of fecal samples at 6 months of age (n = 506, prior to infant supplementation, which extended to 18 months) using 16S rRNA gene sequencing of the V4 region. Features of the gut microbiota previously identified as being involved in fatty acid or micronutrient metabolism or in outcomes relating to growth and inflammation, especially in children, were investigated. Prior to correction for multiple hypothesis testing, the effects of LNS on growth appeared to be modified by Clostridium (p-for-interaction = 0.02), Ruminococcus (p-for-interaction = 0.007), and Firmicutes (p-for-interaction = 0.04) and effects on inflammation appeared to be modified by Faecalibacterium (p-for-interaction = 0.03) and Streptococcus (p-for-interaction = 0.004). However, after correction for multiple hypothesis testing these findings were not statistically significant, suggesting that the gut microbiota did not alter the effect of LNS on infant growth and inflammation in this cohort.

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

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Effect of complementary feeding behavior change communication delivered through community-level actors on the time of initiation of complementary foods in rural communities of West Gojjam zone, Northwest Ethiopia: a cluster-randomized controlled trial

Chalachew Abiyu[1], Tefera Belachew[2]

Abstract

Background: Attaining the recommended level of complementary feeding practices remains a serious challenge in many developing countries. Complementary foods are usually untimely initiated, which has adverse consequences on the growth, development, and survival of infants. The focus of most studies conducted worldwide seemed to be on the effect of behavior change interventions on the adequacy of complementary diets; but not on the timing of initiations. Moreover, many of the interventions targeted only mothers/caregivers of infants, and studies that engaged the family members are scarce. This study aimed to evaluate the effectiveness of complementary feeding behavior change communication delivered through women development army leaderson the time of initiation of complementary foods.

Methods: We conducted a cluster-randomized controlled trial in rural communities of West Gojjam Zone, Northwest Ethiopia from February 2017 to March 2018. A total of 16 geographic clusters were selected. Trial participants in the intervention group received complementary feeding behavior change intervention for 9 months whereas those in the control group received only the usual health care. Trained women development army leaders delivered the intervention. A pre-tested, structured interviewer-administered questionnaire was used for data collection. Generalized estimated equation (GEE) regression and survival analyses were used to test differences in time of initiation of complementary food between the study groups.

Results: The intervention significantly improved the likelihood of timely initiation of complementary food by 22 percentage points [RR: 2.6; 95% CI: 1.78-5.86], and reduced the risk of late initiations by 19 percentage points [RR: 2.8; 95% CI: 1.83-4.37]. The complementary food initiation survival curve for the control group after 6 months was constantly above the curve than for the intervention group. The median age at the introduction of complementary food for infants was 6 months in the intervention group, and 6.7 months in the control group and the difference was statistically significant (P-value < 0.001).

Conclusions: Complementary feeding behavior change communication improved the rate of timely initiation of complementary foods and reduced the risk of late initiations.

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Effect of complementary feeding behavior change communication delivered through community-level actors on dietary adequacy of infants in rural communities of West Gojjam Zone, Northwest Ethiopia: A cluster-randomized controlled trial

Chalachew Abiyu[1], Tefera Belachew[2]

Abstract

Background: Attaining the recommended level of adequacy of the infant's diet remains a serious challenge in most developing countries. Complementary foods, particularly in

developing countries, are inadequate in quality and quantity that can result in adverse health and nutrition consequences in infants. This could be not only because of lack of food but also associated with caregiver's poor knowledge, harmful cultural norms and behaviors on infant feeding. The promotion of optimal complementary feeding through behavior change interventions is a global health priority. However, many of the interventions targeted only mothers/caregivers of infants, and studies that engaged other family members are limited worldwide. Moreover, such interventions are scarce in developing countries, including Ethiopia. This trial aimed to evaluate the effectiveness of complementary feeding behavior change communication delivered through community-level actors on the dietary adequacy of infants.
Methods: We conducted a cluster-randomized controlled trial in rural communities of West Gojjam Zone, Northwest Ethiopia. Trial participants in the intervention clusters received complementary feeding behavior change communication for 9 months whereas those in the control clusters received only the usual care. Trained women development army leaders delivered the intervention. A pre-tested, structured interviewer-administered questionnaire was used for data collection. Generalized estimating equations regression analyses adjusted for baseline covariates and clustering were used to test the intervention effects.
Results: The intervention showed positive statistically significant effects on the consumption of dairy products [RR = 1.8; 95% CI: 1.04-3.13], eggs [RR = 3; 95% CI: 1.35-6.56], vitamin A-rich fruits and vegetables [RR = 2.7; 95% CI: 1.17-6.1], other fruits and vegetables [RR = 5; 95% CI: 2.49-10.58] and animal-source foods [RR = 2; 95% CI: 1.39-2.87]. The proportions of infants who achieved minimum dietary diversity [RR = 3; 95% CI: 1.34, 7.39], minimum meal frequency [RR = 2.4; 95% CI: 1.37-4.29], and minimum acceptable diet [RR = 2.7; 95% CI: 1.13-7.23] were significantly higher in the intervention as compared to control groups.
Conclusions: Complementary feeding behavior change communication delivered through community-level actors significantly improved the dietary adequacy of infants.

Comment. Redundant publication

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doi: 10.1111/mcn.13055. Epub 2020 Jul 20.
Impacts of an egg complementary feeding trial on energy intake and dietary diversity in Malawi
Chessa K Lutter[1], Bess L Caswell[2], Charles D Arnold[2], Lora L Iannotti[3], Kenneth Maleta[4], Raphael Chipatala[4], Elizabeth L Prado[2], Christine P Stewart[2]
Abstract
Complementary feeding diets in low- and middle-income countries are generally inadequate to meet requirements for growth and development. Food-based interventions may prevent nutrient inadequacies provided that they do not displace other nutrient-rich foods. We conducted a randomized controlled trial in rural Malawi in which 660 children aged 6 to 9 months were provided an egg a day for 6 months or assigned to a control group. Dietary

intake of complementary foods and drinks was assessed at baseline, 3-month midline and 6-month endline visits using a tablet-based multipass 24-h recall. Up to two repeat recalls were collected at each time point in a subsample of 100 children per treatment group. At midline and endline, usual energy intake from eggs was about 30 kcal/day higher in the egg group compared with controls ($p < 0.0001$). Compared with controls, children in the egg group were over nine times more likely to consume eggs at midline and endline. There was a comparable, but nonsignificant, greater total usual energy intake from complementary foods of 30 kcal/day at midline ($p = 0.128$) and 36 kcal/day at endline ($p = 0.087$). There also was a displacement of 7 kcal/day in legumes and nuts in children at endline ($p = 0.059$). At midline and endline, more than 80% of children in the egg group consumed a minimally diverse diet compared with 53% at midline and 60% at endline in the control group. This study illustrates that mothers in the egg group fed eggs to young children on a regular basis without substantial displacement of other complementary foods.

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Early Child Development Outcomes of a Randomized Trial Providing 1 Egg Per Day to Children Age 6 to 15 Months in Malawi

Elizabeth L Prado[1], Kenneth Maleta[2], Bess L Caswell[1], Matthews George[2], Lisa M Oakes[3], Michaela C DeBolt[3], Megan G Bragg[1], Charles D Arnold[1], Lora L Iannotti[4], Chessa K Lutter[5], Christine P Stewart[1]

Abstract

Background: Eggs are a rich source of nutrients important for brain development, including choline, riboflavin, vitamins B-6 and B-12, folate, zinc, protein, and DHA.

Objective: Our objective was to evaluate the effect of the consumption of 1 egg per day over a 6-mo period on child development.

Methods: In the Mazira Project randomized controlled trial, 660 children aged 6-9 mo were randomly allocated into an intervention or control group. Eggs were provided to intervention households during twice-weekly home visits for 6 mo. Control households were visited at the same frequency. At enrollment, blinded assessors administered the Malawi Developmental Assessment Tool (MDAT), and 2 eye-tracking tasks using a Tobii-Pro X2-60 eye tracker: a visual paired comparison memory task and an Infant Orienting with Attention task. At endline, 6-mo later, blinded assessors administered the MDAT and eye-tracking tasks plus an additional elicited imitation memory task.

Results: At endline, intervention and control groups did not significantly differ in any developmental score, with the exception that a smaller percentage of children were delayed in fine motor development in the intervention group (10.6%) compared with the control group (16.5%; prevalence ratio: 0.59, 95% CI: 0.38-0.91). Among 10 prespecified effect modifiers for the 8 primary developmental outcomes, we found 7 significant interactions demonstrating a consistent pattern that children who were less vulnerable, for example, those with higher household wealth and maternal education, showed positive effects of the intervention. Given multiple hypothesis testing, some findings may have been due to chance.

Conclusion: The provision of 1 egg per day had no overall effect on child development in this population of children, however, some benefits may be seen among children in less vulnerable circumstances.

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Community-level interventions for improving access to food in low- and middle-income countries

Solange Durao[1], Marianne E Visser[2], Vundli Ramokolo[3], Julicristie M Oliveira[4], Bey-Marrié Schmidt[1], Yusentha Balakrishna[5], Amanda Brand[2], Elizabeth Kristjansson[6], Anel Schoonees[2]

Abstract

Background: After decades of decline since 2005, the global prevalence of undernourishment reverted and since 2015 has increased to levels seen in 2010 to 2011. The prevalence is highest in low- and middle-income countries (LMICs), especially Africa and Asia. Food insecurity and associated undernutrition detrimentally affect health and socioeconomic development in the short and long term, for individuals, including children, and societies. Physical and economic access to food is crucial to ensure food security. Community-level interventions could be important to increase access to food in LMICs.

Objectives: To determine the effects of community-level interventions that aim to improve access to nutritious food in LMICs, for both the whole community and for disadvantaged or at-risk individuals or groups within a community, such as infants, children and women; elderly, poor or unemployed people; or minority groups.

Search methods: We searched for relevant studies in 16 electronic databases, including trial registries, from 1980 to September 2019, and updated the searches in six key databases in February 2020. We applied no language or publication status limits.

Selection criteria: We included randomised controlled trials (RCTs), cluster randomised controlled trials (cRCTs) and prospective controlled studies (PCS). All population groups, adults and children, living in communities in LMICs exposed to community-level interventions aiming to improve food access were eligible for inclusion. We excluded studies that only included participants with specific diseases or conditions (e.g. severely malnourished children). Eligible interventions were broadly categorised into those that improved buying power (e.g. create income-generation opportunities, cash transfer schemes); addressed food prices (e.g. vouchers and subsidies); addressed infrastructure and transport that affected physical access to food outlets; addressed the social environment and provided social support (e.g. social support from family, neighbours or government).

Data collection and analysis: Two authors independently screened titles and abstracts, and full texts of potentially eligible records, against the inclusion criteria. Disagreements were resolved through discussion or arbitration by a third author, if necessary. For each included study, two authors independently extracted data and a third author arbitrated disagreements. However, the outcome data were extracted by one author and checked by a biostatistician. We assessed risk of bias for all studies using the Effective Practice and Organization of Care (EPOC) risk of bias tool for studies with a separate control group. We conducted meta-analyses if there was a minimum of two studies for interventions within the

same category, reporting the same outcome measure and these were sufficiently homogeneous. Where we were able to meta-analyse, we used the random-effects model to incorporate any existing heterogeneity. Where we were unable to conduct meta-analyses, we synthesised using vote counting based on effect direction.
Main results: We included 59 studies, including 214 to 169,485 participants, and 300 to 124, 644 households, mostly from Africa and Latin America, addressing the following six intervention types (three studies assessed two different types of interventions). Interventions that improved buying power: Unconditional cash transfers (UCTs) (16 cRCTs, two RCTs, three PCSs): we found high-certainty evidence that UCTs improve food security and make little or no difference to cognitive function and development and low-certainty evidence that UCTs may increase dietary diversity and may reduce stunting. The evidence was very uncertain about the effects of UCTs on the proportion of household expenditure on food, and on wasting. Regarding adverse outcomes, evidence from one trial indicates that UCTs reduce the proportion of infants who are overweight. Conditional cash transfers (CCTs) (nine cRCTs, five PCSs): we found high-certainty evidence that CCTs result in little to no difference in the proportion of household expenditure on food and that they slightly improve cognitive function in children; moderate-certainty evidence that CCTs probably slightly improve dietary diversity and low-certainty evidence that they may make little to no difference to stunting or wasting. Evidence on adverse outcomes (two PCSs) shows that CCTs make no difference to the proportion of overweight children. Income generation interventions (six cRCTs, 11 PCSs): we found moderate-certainty evidence that income generation interventions probably make little or no difference to stunting or wasting; and low-certainty evidence that they may result in little to no difference to food security or that they may improve dietary diversity in children, but not for households. Interventions that addressed food prices: Food vouchers (three cRCTs, one RCT): we found moderate-certainty evidence that food vouchers probably reduce stunting; and low-certainty evidence that that they may improve dietary diversity slightly, and may result in little to no difference in wasting. Food and nutrition subsidies (one cRCT, three PCSs): we found low-certainty evidence that food and nutrition subsidies may improve dietary diversity among school children. The evidence is very uncertain about the effects on household expenditure on healthy foods as a proportion of total expenditure on food (very low-certainty evidence). Interventions that addressed the social environment: Social support interventions (one cRCT, one PCS): we found moderate-certainty evidence that community grants probably make little or no difference to wasting; low-certainty evidence that they may make little or no difference to stunting. The evidence is very uncertain about the effects of village savings and loans on food security and dietary diversity. None of the included studies addressed the intervention category of infrastructure changes. In addition, none of the studies reported on one of the primary outcomes of this review, namely prevalence of undernourishment.
Authors' conclusions: The body of evidence indicates that UCTs can improve food security. Income generation interventions do not seem to make a difference for food security, but the evidence is unclear for the other interventions. CCTs, UCTs, interventions that help generate income, interventions that help minimise impact of food prices through food vouchers and subsidies can potentially improve dietary diversity. UCTs and food vouchers may have a potential impact on reducing stunting, but CCTs, income generation interventions or social environment interventions do not seem to make a difference on wasting or stunting. CCTs seem to positively impact cognitive function and development, but not UCTs, which may be due to school attendance, healthcare visits and other conditionalities associated with CCTs.

BMC Pediatr. 2020 Sep 1;20(1):412.
doi: 10.1186/s12887-020-02326-z.

Child acceptability of a novel provitamin A carotenoid, iron and zinc-rich complementary food blend prepared from pumpkin and common bean in Uganda: a randomised control trial

Edward Buzigi[1 2 3], Kirthee Pillay[4], Muthulisi Siwela[4]

Abstract

Background: Ugandan children are fed homemade complementary foods (CFs) which are usually deficient in vitamin A, iron and zinc. Novel homemade CFs rich in vitamin A, iron and zinc need to be developed, and assessed for their acceptability among target children.

Objective: Homemade provitamin A carotenoids (PVACs), iron and zinc-rich complementary food (CF), common bean pumpkin blend (BPB) formulated from pumpkin (Sweet cream) and common bean (Obwelu) and PVAC-rich pumpkin blend (PB) from Sweet cream were prepared by expert peer mothers. This study compared child acceptability of BPB and PB (control).

Methods: The crossover acceptability study randomly assigned Ugandan children 6 to 24 months old to either receive 100 g of BPB (n = 35) or 100 g of PB (n = 35) on day one. After a washout period of one day, children crossed over to receive either BPB (n = 35) or PB (n = 35). The amount of CF consumed, duration of consumption, and micronutrient intake were assessed. The CF was acceptable if children consumed ≥50 g (50%) of served food (100 g). A paired t-test was used to determine the mean differences within participants between BPB and PB. The level of statistical significant difference was set at a probability value of 5% ($p = 0.05$).

Results: The mean consumption of BPB and PB was 53.9 g and 54.4 g, respectively. The mean duration for consumption of BPB and PB was 20.6 and 20.3 min, respectively. There was no significant difference in the amounts consumed, and duration of consumption in BPB and PB ($p > 0.05$). The mean intake of vitamin A was significantly higher ($p < 0.00001$) in PB (152.5 µgRAE) compared to BPB (100.9 µgRAE). The mean iron intake was significantly higher in BPB (1.1 mg) ($p < 0.00001$) compared to PB (0.3 mg). Furthermore, zinc intake was significantly higher ($p < 0.00001$) in BPB (0.58 mg) compared to PB (0.13 mg).

Conclusion: A homemade complementary food, BPB, made from locally available common bean and pumpkin is rich in PVACs, iron and zinc and is acceptable to children in the age range of complementary feeding in Uganda.

BMC Public Health. 2020 Sep 22;20(1):1437.
doi: 10.1186/s12889-020-09262-8.

Scaled-up nutrition education on pulse-cereal complementary food practice in Ethiopia: a cluster-randomized trial

Getenesh Berhanu Teshome[1], Susan J Whiting[2], Timothy J Green[3], Demmelash Mulualem[4], Carol J Henry[2]

Abstract

Background: Improving children's weight status through nutrition education (NE) for mothers about using pulses in complementary feeding has been demonstrated in pilot

studies, but no effect on stunting was reported. The aim of the study was to assess the impact of a 9-month pulse-nutrition education program on improving mothers' knowledge, attitude, and practices (KAP) towards pulses, as well as its effect on children's diet diversity, and nutritional status. The NE was delivered by Health Extension Workers (HEWs).
Methods: A cluster randomized study was employed for the community-based interventional study. Twelve randomly selected villages in Sidama Zone, Southern Ethiopia were included in the study. A total of 772 mother-child pairs involved in the study; where 386 mother-child pairs in the intervention group received additional messages about pulse-cereal complementary food, and 386 pairs (the control) received only routine health education for 9 months. A survey on mothers' KAP and anthropometric measurements of the children were taken at baseline, midpoint, and end point. ANOVA and descriptive statistics were used to analyzed data.
Results: At baseline and end point, maternal KAP and the dietary diversity score of the children (mean age at end point 18.8 ± 2.9 mo) were assessed. Intervention mothers' KAP improved ($p < 0.001$) at midpoint and end point compared to that of the control group, as did frequency of pulse consumption and Dietary Diversity Score (DDS) among children. At 9 months, the prevalence of stunting, wasting, and underweight was significantly reduced in the intervention group compared to the control group ($p = 0.001$).
Conclusions: NE delivered by HEWs improved KAP of mothers regarding pulse consumption and dietary diversity of children led to improved nutritional status of the children. Training HEWs on the use of pulses for complementary food may be an effective way to improve the health of children in Ethiopian communities.

Int J Environ Res Public Health. 2020 Sep 23;17(19):6970.
doi: 10.3390/ijerph17196970.
Nutrition Education Intervention Increases Fish Consumption among School Children in Indonesia: Results from Behavioral Based Randomized Control Trial
Trias Mahmudiono[1,2], Triska Susila Nindya[1], Qonita Rachmah[1], Calista Segalita[1], Luh Ade Ari Wiradnyani[2]
Abstract
This study aimed to analyze the effectiveness of behavioral-based nutrition education to increase fish consumption among school children using a raised bed pool. This was a randomized control trial study with a 3-months nutrition education intervention using a raised bed pool, as a medium to improve their internalization to increase fish consumption behavior. A paired *t*-test was used to calculate the difference in the increase of fish consumption, knowledge, attitude, perceived behavioral control, subjective norm, and intention. This study took place in a majority of low to medium urban households in Surabaya in Sidotopo Wetan I and Sidotopo Wetan II elementary school. Elementary school children at 4th and 5th grade and mother of elementary school children with 104 children were eligible and willing to participate. After the completion of interventions, significant improvement in delta-mean and effectiveness observed in attitude, subjective norm, perceived behavioral control, intention, knowledge, and fish consumption ($p < 0.001$). The 3 months of nutrition education intervention based on the theory of planned behavior significantly increase fish consumption among elementary school children. The increased

consumption was believed to be related to the increase in children's knowledge and attitude towards consuming fish.

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Tubaramure, a Food-Assisted Integrated Health and Nutrition Program, Reduces Child Wasting in Burundi: A Cluster-Randomized Controlled Intervention Trial

Jef L Leroy[1], Deanna K Olney[1], Noé Nduwabike[2], Marie T Ruel[1]

Abstract

Background: Little is known about the impact of food-assisted maternal and child health programs (FA-MCHN) on child wasting.

Objectives: We assessed the impact of Tubaramure, a FA-MCHN program in Burundi, on child (0 to 24 months) wasting and the differential impacts by socio-economic characteristics and age. The program targeted women and their children during the first 1000 days and included 1) food rations, 2) strengthening and promotion of use of health services, and 3) behavior change communication (BCC).

Methods: We conducted a 4-arm, cluster-randomized, controlled trial (2010-2012). Clusters were defined as "collines" (communities). Impact was estimated using repeated cross-sectional data (n = ~2620 children in each round). Treatment arms received household and individual (mother or child in the first 1000 days) food rations (corn-soy blend and micronutrient-fortified vegetable oil) from pregnancy to 24 months (T24 arm), from pregnancy to 18 months (T18), or from birth to 24 months (TNFP). All beneficiaries received the same BCC for the first 1000 days. The control arm received no rations or BCC.

Results: Wasting (weight-for-length Z-score <2 SD) increased from baseline to follow-up in the control group (from 6.5% to 8%), but Tubaramure had a significant ($P < 0.05$) protective effect on wasting [treatment arms combined, -3.3 percentage points (pp); T18, -4.5 pp] and on the weight-for-length z-score (treatment arms combined, +0.15; T24, +0.20; T18, +0.17). The effects were limited to children whose mother and household head had no education, and who lived in the poorest households. The largest effect was found in children 6 to 12 months of age: the group with the highest wasting prevalence.

Conclusions: FA-MCHN programs in highly food-insecure regions can protect the most disadvantaged children from wasting. These findings are particularly relevant in the context of the economic crisis due to the coronavirus disease 2019 pandemic, which is expected to dramatically increase child wasting.

Breastfeeding

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Breastfeeding Education and Support to Improve Early Initiation and Exclusive Breastfeeding Practices and Infant Growth: A Cluster Randomized Controlled Trial from a Rural Ethiopian Setting

Misra Abdulahi[1,2], Atle Fretheim[3,4], Alemayehu Argaw[1,5], Jeanette H Magnus[6,7]

Abstract

Although peer-led education and support may improve breastfeeding practices, there is a paucity of evidence on the effectiveness of such interventions in the Ethiopian context. We designed a cluster-randomized trial to evaluate the efficacy of a breastfeeding education and support intervention (BFESI) on infant growth, early initiation (EI), and exclusive breastfeeding (EBF) practices. We randomly assigned 36 clusters into either an intervention group (n = 249) receiving BFESI by trained Women's Development Army (WDA) leaders or a control group (n = 219) receiving routine care. The intervention was provided from the third trimester of pregnancy until five months postpartum. Primary study outcomes were EI, EBF, and infant growth; secondary outcomes included maternal breastfeeding knowledge and attitude, and child morbidity. The intervention effect was analysed using linear regression models for the continuous outcomes, and linear probability or logistic regression models for the categorical outcomes. Compared to the control, BFESI significantly increased EI by 25.9% (95% CI: 14.5, 37.3%; p = 0.001) and EBF by 14.6% (95% CI: 3.77, 25.5%; p = 0.010). Similarly, the intervention gave higher breastfeeding attitude scores (Effect size (ES): 0.85SD; 95% CI: 0.70, 0.99SD; p < 0.001), but not higher knowledge scores (ES: 0.15SD; 95% CI: -0.10, 0.41SD; p = 0.173). From the several growth and morbidity outcomes evaluated, the only outcomes with significant intervention effect were a higher mid-upper arm circumference (ES: 0.25cm; 95% CI: 0.01, 0.49cm; p = 0.041) and a lower prevalence of respiratory infection (ES: -6.90%; 95% CI: -13.3, -0.61%; p = 0.033). Training WDA leaders to provide BFESI substantially improves EI and EBF practices and attitude towards breastfeeding.

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Effectiveness of the baby-friendly community initiative on exclusive breastfeeding in Kenya

Elizabeth W Kimani-Murage[1,2], Judith Kimiywe[3], Antonina N Mutoro[1,4], Calistus Wilunda[1], Frederick Murunga Wekesah[1], Peter Muriuki[1], Bonaventure M Mwangi[1], Betty Mogesi Samburu[5,6], Nyovani Janet Madise[7], Stephen T McGarvey[2], Paula L Griffiths[8,9]

Abstract

The baby-friendly hospital initiative (BFHI) promotes exclusive breastfeeding (EBF) in hospitals, but this is not accessible in rural settings where mothers give birth at home, hence the need for a community intervention. We tested the effectiveness of the baby-friendly community initiative (BFCI) on EBF in rural Kenya. This cluster randomized study was conducted in 13 community units in Koibatek sub-county. Pregnant women aged 15-49 years were recruited and followed up until their children were 6 months old. Mothers in the intervention group received standard maternal, infant and young child nutrition counselling, support from trained community health volunteers, health professionals and community and mother support groups, whereas those in the control group received standard counselling only. Data on breastfeeding practices were collected longitudinally. The probability of EBF up to 6 months of age and the restricted mean survival time difference

were estimated. A total of 823 (intervention group n = 351) pregnant women were recruited. Compared with children in the control group, children in the intervention group were more likely to exclusively breastfeed for 6 months (79.2% vs. 54.5%; P < .05). Children in the intervention group were also exclusively breastfed for a longer time, mean difference (95% confidence interval [CI]) 0.62 months (0.38, 0.85; P < .001). The BFCI implemented within the existing health system and including community and mother support groups led to a significant increase in EBF in a rural Kenyan setting. This intervention has the potential to improve EBF rates in similar settings.

Int Breastfeed J. 2020 Jul 14;15(1):62.
doi: 10.1186/s13006-020-00299-4.

Effectiveness of the baby-friendly community initiative in promoting exclusive breastfeeding among HIV negative and positive mothers: a randomized controlled trial in Koibatek Sub-County, Baringo, Kenya

Betty Mogesi Samburu[1,2], Sera Lewise Young[3], Frederick Murunga Wekesah[4,5], Milkah Njeri Wanjohi[4], Judith Kimiywe[6], Peter Muriuki[4,7], Paula L Griffiths[8], Stephen T McGarvey[9], Nyovani Janet Madise[10], Elizabeth W Kimani-Murage[4,9,11,12,13]

Abstract

Background: Although the baby-friendly community initiative (BFCI) has been proposed as a community-level approach to improve infant feeding practices, there is little data on its variation in effectiveness by HIV status. We conducted a study to determine the effectiveness of BFCI in changing knowledge and attitudes towards exclusive breastfeeding (EBF) and increasing the rates among HIV negative and HIV positive women in rural Kenya.

Methods: A community-based cluster-randomized controlled trial was implemented from April 2015 to December 2016 among 901 women enrolled across 13 clusters. The intervention groups received a minimum of 12 personalized home-based counselling sessions on infant feeding by trained community health volunteers from their first or second trimester of pregnancy until 6 months postpartum. Other interventions included education sessions at maternal child clinics, mother-to-mother support group meetings and bi-monthly baby-friendly gatherings targeting influencers. The control group received standard health education at the facility and during monthly routine home visits by community health volunteers not trained on BFCI. Primary outcome measures were the rates of EBF at week 1, months 2, 4 and 6 postpartum. Secondary outcomes included knowledge and attitudes regarding breastfeeding for HIV-exposed infants. Statistical methods included analysis of covariance and logistic regression.

Results: At 6 months, EBF rates among HIV negative mothers were significantly higher in the BFCI intervention arm compared to the control arm (81.7% versus 42.2% p = 0.001). HIV positive mothers in the intervention arm had higher EBF rates at 6 months than the control but the difference was not statistically significant (81.8% versus 58.4%; p = 0.504). In HIV negative group, there was greater knowledge regarding EBF for HIV-exposed infants in the intervention arm than in the control (92.1% versus 60.7% p = 0.001). Among HIV positive mothers, such knowledge was high among both the intervention and control groups (96% versus 100%, p > 0.1). HIV negative and positive mothers in the intervention arm had more favourable attitudes regarding EBF for HIV-exposed infants than the control (84.5% versus 62.1%, p = 0.001) and (94.6% versus 53.8% to p = 0.001) respectively.

Conclusions: BFCI interventions can complement facility-based interventions to improve exclusive and continued breastfeeding knowledge, attitudes, and behaviours among HIV negative and positive women.

Int Breastfeed J. 2020 Sep 1;15(1):77.
doi: 10.1186/s13006-020-00317-5.

Infant feeding knowledge and practice vary by maternal HIV status: a nested cohort study in rural South Africa

H Manisha Yapa[1,2], Róisín Drayne[3], Nigel Klein[4,5], Jan-Walter De Neve[6], Kathy Petoumenos[7], Awachana Jiamsakul[7], Carina Herbst[4], Deenan Pillay[4,8], Frank A Post[9], Till Bärnighausen[4,6,10,11]

Abstract

Background: We investigate whether correct infant feeding knowledge and practice differ by maternal HIV status in an era of evolving clinical guidelines in rural South Africa.

Methods: This cohort study was nested within the MONARCH stepped-wedge cluster-randomised controlled trial (www.clinicaltrials.gov : NCT02626351) which tested the impact of continuous quality improvement on antenatal care quality at seven primary care clinics in KwaZulu-Natal, from July 2015 to January 2017. Women aged ≥18 years at delivery were followed up to 6 weeks postpartum. Clinical data were sourced from routine medical records at delivery. Structured interviews at early postnatal visits and the 6-week postnatal immunisation visit provided data on infant feeding knowledge and feeding practices respectively. We measured the relationship between maternal HIV status and (i) correct infant feeding knowledge at the early postnatal visit; and (ii) infant feeding practice at 6 weeks, using Poisson and multinomial regression models, respectively.

Results: We analysed data from 1693 women with early postnatal and 471 with 6-week postnatal interviews. HIV prevalence was 47% (95% confidence interval [CI] 42, 52%). Women living with HIV were more knowledgeable than women not living with HIV on correct infant feeding recommendations (adjusted risk ratio, aRR, 1.08, $p < 0.001$). More women living with HIV (33%; 95% CI 26, 41%) were not breastfeeding than women not living with HIV (15%; 95% CI 11, 21%). However, among women who were currently breastfeeding their infants, fewer women living with HIV (5%; 95% CI 2, 9%) mixed fed their babies than women not living with HIV (21%; 95% CI 14, 32%). In adjusted analyses, women living with HIV were more likely to avoid breastfeeding (adjusted relative risk ratio, aRRR, 2.78, $p < 0.001$) and less likely to mixed feed (aRRR 0.22, $p < 0.001$) than women not living with HIV.

Conclusions: Many mothers in rural South Africa still do not practice exclusive breastfeeding. Women living with HIV were more knowledgeable but had lower overall uptake of breastfeeding, compared with women not living with HIV. Women living with HIV were also more likely to practice exclusive breastfeeding over mixed feeding if currently breastfeeding. Improved approaches are needed to increase awareness of correct infant feeding and exclusive breastfeeding uptake.

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doi: 10.1038/s41430-020-00798-x. Epub 2020 Nov 6.

Effect of fish-oil supplementation on breastmilk long-chain polyunsaturated fatty acid concentration: a randomized controlled trial in rural Ethiopia

Alemayehu Argaw[#1,2], Kimberley P Bouckaert[#3], Mekitie Wondafrash[4,3], Patrick Kolsteren[3], Carl Lachat[3], Bruno De Meulenaer[3], Giles Hanley-Cook[3], Lieven Huybregts[5]

Abstract

Background: For infants and young children in low-income settings, human milk (HM) is the main source of omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). However, the n-3 LCPs concentrations of HM show wide variability, largely depending on the maternal intake of marine foods. This may put children living far from coastal areas at risk of inadequate intake. We evaluated the efficacy of fish-oil (FO) supplementation of lactating mothers on HM n-3 LCPs concentrations in a rural setting from Ethiopia.

Methods: Mothers (n = 360) with children 6-12 months old were randomized to receive either intervention FO capsules (215 mg DHA + 285 mg EPA) or control corn-oil capsules (without n-3 LCPs). In a random subsample of 154 participants, we analyzed LCPs in HM and child capillary blood using gas chromatography.

Results: Compared to the control, FO supplementation increased HM concentrations of DHA by 39.0% (95% CI: 20.6, 57.5%; P < 0.001) and EPA by 36.2% (95% CI: 16.0, 56.4%; P < 0.001), whereas the arachidonic acid (AA)/(DHA + EPA) ratio decreased by 53.5% (95% CI: -70.2, -36.7%; P < 0.001). We also found statistically significant association between the changes in (DHA + EPA)/AA ratio in HM and child capillary blood (P < 0.001). However, HM DHA concentrations remained lower than international norms after FO supplementation.

Conclusions: FO supplementation improves n-3 LCPs content of HM. Future studies should evaluate different doses of n-3 LCPs and consider potential effect modifiers such as genetic polymorphism and diet.

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Associations of human milk oligosaccharides and bioactive proteins with infant growth and development among Malawian mother-infant dyads

Josh M Jorgensen[1], Rebecca Young[1], Per Ashorn[2,3], Ulla Ashorn[2], David Chaima[4], Jasmine C C Davis[5], Elisha Goonatilleke[5], Chiza Kumwenda[4,6], Carlito B Lebrilla[5,7], Kenneth Maleta[4], Elizabeth L Prado[1], John Sadalaki[4], Sarah M Totten[5], Lauren D Wu[5], Angela M Zivkovic[1,8], Kathryn G Dewey[1]

Abstract

Background: Human milk oligosaccharides (HMOs) and bioactive breast milk proteins have many beneficial properties. Information is sparse regarding associations between these milk constituents and infant growth and development in lower-income countries.

Objectives: We aimed to examine associations of milk content of HMOs and bioactive proteins at 6 mo postpartum with infant growth and motor and cognitive development. These are secondary analyses of a randomized controlled trial in rural Malawi.

Methods: Breast milk samples were analyzed at 6 mo (n = 659) for general categories of HMOs (total HMOs, fucosylated HMOs, and sialylated HMOs), 51 individual HMOs, and 6

bioactive proteins (lactalbumin, lactoferrin, lysozyme, antitrypsin, IgA, and osteopontin). We examined associations of the relative abundances of HMOs and concentrations of bioactive proteins with infant growth from 6 to 12 mo [change in length-for-age (ΔLAZ), weight-for-age, weight-for-length, and head circumference z-scores] as well as ability to stand or walk alone at 12 mo, and motor and language skills, socioemotional development, executive function, and working memory at 18 mo. Analyses were adjusted for covariates and multiple hypothesis testing.
Results: Among all participants, there were inverse associations of IgA and lactoferrin concentrations with motor skills (P = 0.018 and P = 0.044), and a positive association of lactalbumin concentration with motor skills (P = 0.038). Among secretors only [fucosyltransferase 2 gene (FUT2) positive], there were positive associations of absolute abundance of HMOs with ΔLAZ (P = 0.035), and relative abundance of fucosylated and sialylated HMOs with language at 18 mo (P < 0.001 and P = 0.033, respectively), and inverse associations of osteopontin with standing and walking at 12 mo (P = 0.007 and 0.002, respectively). Relative abundances of several individual HMOs were associated with growth and development, mostly among secretors.
Conclusions: Certain bioactive breast milk proteins and HMOs are associated with infant growth and motor and cognitive development. Further studies are needed to determine if a causal relation exists.

Community nutrition and agriculture

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A Nutrition-Sensitive Agroecology Intervention in Rural Tanzania Increases Children's Dietary Diversity and Household Food Security But Does Not Change Child Anthropometry: Results from a Cluster-Randomized Trial
Marianne V Santoso[1,2], Rachel N Bezner Kerr[3], Neema Kassim[4], Haikael Martin[4], Elias Mtinda[5], Peter Njau[6], Kelvin Mtei[4], John Hoddinott[1,7], Sera L Young[2,8]
Abstract
Background: There are urgent calls for the transformation of agriculture and food systems to address human and planetary health issues. Nutrition-sensitive agriculture and agroecology promise interconnected solutions to these challenges, but evidence of their impact has been limited.
Objectives: In a cluster-randomized trial (NCT02761876), we examined whether a nutrition-sensitive agroecology intervention in rural Tanzania could improve children's dietary diversity. Secondary outcomes were food insecurity and child anthropometry. We also posited that such an intervention would improve sustainable agricultural practices (e.g., agrobiodiversity, intercropping), women's empowerment (e.g., participation in decision making, time use), and women's well-being (e.g., dietary diversity, depression).
Methods: Food-insecure smallholder farmers with children aged <1 y from 20 villages in Singida, Tanzania, were invited to participate. Villages were paired and publicly randomized; control villages received the intervention after 2 y. One man and 1 woman "mentor farmer" were elected from each intervention village to lead their peers in agroecological learning on

topics including legume intensification, nutrition, and women's empowerment. Impact was estimated using longitudinal difference-in-differences fixed-effects regression analyses.
Results: A total of 591 households (intervention: n = 296; control: n = 295) were enrolled; 90.0% were retained to study end. After 2 growing seasons, the intervention improved children's dietary diversity score by 0.57 food groups (out of 7; P < 0.01), and the percentage of children achieving minimum dietary diversity (≥4 food groups) increased by 9.9 percentage points during the postharvest season. The intervention significantly reduced household food insecurity but had no significant impact on child anthropometry. The intervention also improved a range of sustainable agriculture, women's empowerment, and women's well-being outcomes.
Conclusions: The magnitude of the intervention's impacts was similar to or larger than that of other nutrition-sensitive interventions that provided more substantial inputs but were not agroecologically focused. These data suggest the untapped potential for nutrition-sensitive agroecological approaches to achieve human health while promoting sustainable agricultural practices.

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Nudging children toward healthier food choices: An experiment combining school and home gardens

Pepijn Schreinemachers[1], Ghassan Baliki[2], Rachana Manandhar Shrestha[3], Dhruba Raj Bhattarai[4], Ishwori P Gautam[5], Puspa Lal Ghimire[6], Bhishma P Subedi[6], Tilman Brück[2 7 8]

Abstract
School gardens have become a widely used approach to influence children's food knowledge, preferences and choices in low- and high-income countries alike. However, evidence indicates that such programs are more effective at influencing food knowledge and preferences than actual food choices. Such finding may occur because school gardens insufficiently influence the food behavior of parents and because healthy food items are not always available in children's homes. We tested this hypothesis using a one-year cluster randomized controlled trial in Nepal with 15 treatment and 15 control schools and a matched sample of 779 schoolchildren (aged 8-12) and their caregivers. Data were collected before and after the intervention during the 2018-2019 school year. In addition, children's food consumption was monitored using a monthly food logbook. Average treatment effects were quantified with a double-difference estimator. For caregivers, the intervention led to a 26% increase in their food and nutrition knowledge (p < 0.001), a 5% increase in their agricultural knowledge (p = 0.022), a 10% increase in their liking for vegetables (p < 0.001), and a 15% increase in home garden productivity (p = 0.073). For children, the intervention had no discernible effect on food and nutrition knowledge (p = 0.666) but led to a 6% increase in their liking for vegetables (p = 0.070), healthy food practices (p < 0.001), and vegetable consumption (October-December +15%; p = 0.084; January-March +26%; p = 0.017; April-June +26%; p = 0.088). The results therefore indicate both schools and parents matter for nudging children toward healthier food choices.

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A Chicken Production Intervention and Additional Nutrition Behavior Change Component Increased Child Growth in Ethiopia: A Cluster-Randomized Trial

Simone Passarelli[1], Ramya Ambikapathi[2], Nilupa S Gunaratna[2], Isabel Madzorera[1], Chelsey R Canavan[1], Abdallah R Noor[1], Amare Worku[3], Yemane Berhane[3], Semira Abdelmenan[3], Simbarashe Sibanda[4], Bertha Munthali[4], Tshilidzi Madzivhandila[4], Lindiwe M Sibanda[4], Kumlachew Geremew[5], Tadelle Dessie[5], Solomon Abegaz[6], Getnet Assefa[6], Christopher Sudfeld[7], Margaret McConnell[7], Kirsten Davison[8], Wafaie Fawzi[7]

Abstract

Background: Chicken production in the context of nutrition-sensitive agriculture may benefit child nutrition in low-income settings.

Objectives: This study evaluated effects of 1) a chicken production intervention [African Chicken Genetic Gains (ACGG)], and 2) the ACGG intervention with nutrition-sensitive behavior change communication (BCC) [ACGG + Agriculture to Nutrition (ATONU)], on child nutrition and health outcomes and hypothesized intermediaries.

Methods: Forty ACGG villages received 25 genetically improved chickens and basic husbandry guidance; of these, 20 ACGG + ATONU villages in addition received a nutrition-sensitive behavior change and homegardening intervention; 20 control clusters received no intervention. We assessed effects of the interventions on height-for-age z scores (HAZ), weight-for-age z scores (WAZ), and weight-for-height z scores (WHZ) at 9 (midline) and 18 mo (endline) through unadjusted and adjusted ordinary least squares (OLS) regressions. We examined the interventions' effects on hypothesized intermediaries including egg production and consumption, dietary diversity, women's empowerment, income, child morbidities, anemia, and chicken management practices through OLS and log binomial models.

Results: Data included 829 children aged 0-36 mo at baseline. ACGG + ATONU children had higher midline HAZ [mean difference (MD): 0.28; 95% CI: 0.02, 0.54] than controls. The ACGG group had higher HAZ (MD: 0.28; 95% CI: 0.05, 0.50) and higher WAZ (MD: 0.18; 95% CI: 0.01, 0.36) at endline than controls; after adjusting for potential baseline imbalance, effects were similar but not statistically significant. At endline, differences in ACGG + ATONU children's HAZ and WAZ compared with controls were similar in magnitude to those of ACGG, but not statistically significant. There were no differences in anthropometry between the intervention groups. ACGG + ATONU children had higher dietary diversity and egg consumption than ACGG children at endline. Both interventions showed improvements in chicken management practices. The interventions did not increase anemia, diarrhea, fever, or vomiting, and the ACGG + ATONU group at midline showed reduced risk of fever.

Conclusions: A chicken production intervention with or without nutrition-sensitive BCC may have benefited child nutrition and did not increase morbidity

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Home gardening improves dietary diversity, a cluster-randomized controlled trial among Tanzanian women

Mia M Blakstad[1], Dominic Mosha[2], Alexandra L Bellows[1], Chelsey R Canavan[1], Jarvis T Chen[3], Killian Mlalama[2], Ramadhani A Noor[4], Joyce Kinabo[5], Honorati Masanja[2], Wafaie W Fawzi[1,4,6]

Abstract

Homestead food production (HFP) programmes improve the availability of vegetables by providing training in growing nutrient-dense crops. In rural Tanzania, most foods consumed are carbohydrate-rich staples with low micronutrient concentrations. This cluster-randomized controlled trial investigated whether women growing home gardens have higher dietary diversity, household food security or probability of consuming nutrient-rich food groups than women in a control group. We enrolled 1,006 women of reproductive age in 10 villages in Pwani Region in eastern Tanzania, split between intervention (INT) and control (CON) groups. INT received (a) agricultural training and inputs to promote HFP and dietary diversity and (b) nutrition and public health counselling from agricultural extension workers and community health workers. CON received standard services provided by agriculture and health workers. Results were analysed using linear regression models with propensity weighting adjusting for individual-level confounders and differential loss to follow up. Women in INT consumed 0.50 (95% CI [0.20, 0.80], p = 0.001) more food groups per day than women in CON. Women in INT were also 14 percentage points (95% CI [6, 22], p = 0.001) more likely to consume at least five food groups per day, and INT households were 6 percentage points (95% CI [-13, 0], p = 0.059) less likely to experience moderate-to-severe food insecurity compared with CON. This home gardening intervention had positive effects on diet quality and food security after 1 year. Future research should explore whether impact is sustained over time as well as the effects of home garden interventions on additional measures of nutritional status.

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Effect of nutrition-sensitive agriculture interventions with participatory videos and women's group meetings on maternal and child nutritional outcomes in rural Odisha, India (UPAVAN trial): a four-arm, observer-blind, cluster-randomised controlled trial

Suneetha Kadiyala[1], Helen Harris-Fry[2], Ronali Pradhan[3], Satyanarayan Mohanty[4], Shibanath Padhan[5], Suchitra Rath[6], Philip James[2], Emily Fivian[2], Peggy Koniz-Booher[7], Nirmala Nair[6], Hassan Haghparast-Bidgoli[8], Naba Kishor Mishra[5], Shibanand Rath[6], Emma Beaumont[9], Heather Danton[7], Sneha Krishnan[10], Manoj Parida[4], Meghan O'Hearn[11], Abhinav Kumar[3], Avinash Upadhyay[3], Prasanta Tripathy[6], Jolene Skordis[8], Joanna Sturgess[9], Diana Elbourne[9], Audrey Prost[8], Elizabeth Allen[9]

Abstract

Background: Almost a quarter of the world's undernourished people live in India. We tested the effects of three nutrition-sensitive agriculture (NSA) interventions on maternal and child nutrition in India.

Methods: We did a parallel, four-arm, observer-blind, cluster-randomised trial in Keonjhar district, Odisha, India. A cluster was one or more villages with a combined minimum

population of 800 residents. The clusters were allocated 1:1:1:1 to a control group or an intervention group of fortnightly women's groups meetings and household visits over 32 months using: NSA videos (AGRI group); NSA and nutrition-specific videos (AGRI-NUT group); or NSA videos and a nutrition-specific participatory learning and action (PLA) cycle meetings and videos (AGRI-NUT+PLA group). Primary outcomes were the proportion of children aged 6-23 months consuming at least four of seven food groups the previous day and mean maternal body-mass index (BMI). Secondary outcomes were proportion of mothers consuming at least five of ten food groups and child wasting (proportion of children with weight-for-height Z score SD <-2). Outcomes were assessed in children and mothers through cross-sectional surveys at baseline and at endline, 36 months later. Analyses were by intention to treat. Participants and intervention facilitators were not blinded to allocation; the research team were. This trial is registered at ISRCTN, ISRCTN65922679.
Findings: 148 of 162 clusters assessed for eligibility were enrolled and randomly allocated to trial groups (37 clusters per group). Baseline surveys took place from Nov 24, 2016, to Jan 24, 2017; clusters were randomised from December, 2016, to January, 2017; and interventions were implemented from March 20, 2017, to Oct 31, 2019, and endline surveys done from Nov 19, 2019, to Jan 12, 2020, in an average of 32 households per cluster. All clusters were included in the analyses. There was an increase in the proportion of children consuming at least four of seven food groups in the AGRI-NUT (adjusted relative risk [RR] 1·19, 95% CI 1·03 to 1·37, p=0·02) and AGRI-NUT+PLA (1·27, 1·11 to 1·46, p=0·001) groups, but not AGRI (1·06, 0·91 to 1·23, p=0·44), compared with the control group. We found no effects on mean maternal BMI (adjusted mean differences vs control, AGRI -0·05, -0·34 to 0·24; AGRI-NUT 0·04, -0·26 to 0·33; AGRI-NUT+PLA -0·03, -0·3 to 0·23). An increase in the proportion of mothers consuming at least five of ten food groups was seen in the AGRI (adjusted RR 1·21, 1·01 to 1·45) and AGRI-NUT+PLA (1·30, 1·10 to 1·53) groups compared with the control group, but not in AGRI-NUT (1·16, 0·98 to 1·38). We found no effects on child wasting (adjusted RR vs control, AGRI 0·95, 0·73 to 1·24; AGRI-NUT 0·96, 0·72 to 1·29; AGRI-NUT+PLA 0·96, 0·73 to 1·26).
Interpretation: Women's groups using combinations of NSA videos, nutrition-specific videos, and PLA cycle meetings improved maternal and child diet quality in rural Odisha, India. These components have been implemented separately in several low-income settings; effects could be increased by scaling up together.

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Effects on childhood infections of promoting safe and hygienic complementary-food handling practices through a community-based programme: A cluster randomised controlled trial in a rural area of The Gambia

Semira Manaseki-Holland[1], Buba Manjang[1,2], Karla Hemming[1], James T Martin[1], Christopher Bradley[3], Louise Jackson[1], Makie Taal[4], Om Prasad Gautam[5], Francesca Crowe[1], Bakary Sanneh[6], Jeroen Ensink[7], Tim Stokes[8], Sandy Cairncross[7]

Abstract

Background: The Gambia has high rates of under-5 mortality from diarrhoea and pneumonia, peaking during complementary-feeding age. Community-based interventions may reduce complementary-food contamination and disease rates.
Methods and findings: A public health intervention using critical control points and motivational drivers, delivered February-April 2015 in The Gambia, was evaluated in a cluster

randomised controlled trial at 6- and 32-month follow-up in September-October 2015 and October-December 2017, respectively. After consent for trial participation and baseline data were collected, 30 villages (clusters) were randomly assigned to intervention or control, stratified by population size and geography. The intervention included a community-wide campaign on days 1, 2, 17, and 25, a reminder visit at 5 months, plus informal community-volunteer home visits. It promoted 5 key complementary-food and 1 key drinking-water safety and hygiene behaviours through performing arts, public meetings, and certifications delivered by a team from local health and village structures to all villagers who attended the activities, to which mothers of 6- to 24-month-old children were specifically invited. Control villages received a 1-day campaign on domestic-garden water use. The background characteristics of mother and clusters (villages) were balanced between the trial arms. Outcomes were measured at 6 and 32 months in a random sample of 21-26 mothers per cluster. There were no intervention or research team visits to villages between 6 and 32 months. The primary outcome was a composite outcome of the number of times key complementary-food behaviours were observed as a proportion of the number of opportunities to perform the behaviours during the observation period at 6 months. Secondary outcomes included the rate of each recommended behaviour; microbiological growth from complementary food and drinking water (6 months only); and reported acute respiratory infections, diarrhoea, and diarrhoea hospitalisation. Analysis was by intention-to-treat analysis adjusted by clustering. (Registration: PACTR201410000859336). We found that 394/571 (69%) of mothers with complementary-feeding children in the intervention villages were actively involved in the campaign. No villages withdrew, and there were no changes in the implementation of the intervention. The intervention improved behaviour adoption significantly. For the primary outcome, the rate was 662/4,351(incidence rate [IR] = 0.15) in control villages versus 2,861/4,378 (IR = 0.65) in intervention villages (adjusted incidence rate ratio [aIRR] = 4.44, 95% CI 3.62-5.44, p < 0.001), and at 32 months the aIRR was 1.17 (95% CI 1.07-1.29, p = 0.001). Secondary health outcomes also improved with the intervention: (1) mother-reported diarrhoea at 6 months, with adjusted relative risk (aRR) = 0.39 (95% CI 0.32-0.48, p < 0.001), and at 32 months, with aRR = 0.68 (95% CI 0.48-0.96, p = 0.027); (2) mother-reported diarrhoea hospitalisation at 6 months, with aRR = 0.35 (95% CI 0.19-0.66, p = 0.001), and at 32 months, with aRR = 0.38 (95% CI 0.18-0.80, p = 0.011); and (3) mother-reported acute respiratory tract infections at 6 months, with aRR = 0.67 (95% CI 0.53-0.86, p = 0.001), though at 32 months improvement was not significant (p = 0.200). No adverse events were reported. The main limitations were that only medium to small rural villages were involved. Obtaining laboratory cultures from food at 32 months was not possible, and no stool microorganisms were investigated.

Conclusions: We found that low-cost and culturally embedded behaviour change interventions were acceptable to communities and led to short- and long-term improvements in complementary-food safety and hygiene practices, and reported diarrhoea and acute respiratory tract infections.

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Effect of complementary feeding behaviour change communication delivered through community-level actors on infant growth and morbidity in rural communities of West Gojjam Zone, Northwest Ethiopia: A cluster-randomized controlled trial

Chalachew Abiyu Ayalew[1], Tefera Belachew[1]

Abstract

Attaining the recommended level of adequacy of the infants' diet remains a serious challenge in developing countries. On the other hand, the incidence of growth faltering and morbidity increases significantly at 6 months of age when complementary foods are being introduced. This trial aimed to evaluate the effect of complementary feeding behaviour change communication delivered through community-level actors on infant growth and morbidity. We conducted a cluster-randomized controlled trial in rural communities of Ethiopia. Trial participants in the intervention clusters (eight clusters) received complementary feeding behaviour change communication for 9 months, whereas those in the control clusters (eight clusters) received only the usual care. A pre-tested, structured interviewer-administered questionnaire was used for data collection. Generalized estimating equations regression analyses adjusted for baseline covariates and clustering were used to test the effects of the intervention on infant growth and morbidity. Infants in the intervention group had significantly higher weight gain (MD: 0.46 kg; 95% CI: 0.36-0.56) and length gain (MD: 0.96 cm; 95% CI: 0.56-1.36) as compared with those in the control group. The intervention also significantly reduced the rate of infant stunting by 7.5 percentage points (26.5% vs. 34%, RR = 0.68; 95% CI: 0.47-0.98) and underweight by 8.2 percentage points (17% vs. 25.2%; RR = 0.55; 95% CI: 0.35-0.87). Complementary feeding behaviour change communication delivered through community-level actors significantly improved infant weight and length gains and reduced the rate of stunting and underweight.

Nutrients. 2020 Dec 16;12(12):3851.
doi: 10.3390/nu12123851.

Effect of an Integrated Package of Nutrition Behavior Change Interventions on Infant and Young Child Feeding Practices and Child Growth from Birth to 18 Months: Cohort Evaluation of the Baduta Cluster Randomized Controlled Trial in East Java, Indonesia

Umi Fahmida[1], Min Kyaw Htet[1 2 3], Elaine Ferguson[4], Tran Thanh Do[5], Annas Buanasita[6], Christiana Titaley[7], Ashraful Alam[2], Aang Sutrisna[8], Mu Li[2], Iwan Ariawan[9], Michael John Dibley[2]

Abstract

The need for a multisectoral approach to tackle stunting has gained attention in recent years. Baduta project aims to address undernutrition among children during their first 1000 days of life using integrated nutrition-specific and nutrition-sensitive interventions. We undertook this cohort study to evaluate the Baduta project's effectiveness on growth among children under 2 years of age in two districts (Sidoarjo and Malang Districts) in East Java. Six subdistricts were randomly selected, in which three were from the intervention areas, and three were from the control areas. We recruited 340 pregnant women per treatment group during the third trimester of pregnancy and followed up until 18 months postpartum. The assessment of breastfeeding and complementary feeding practices used standard infant and young child feeding (IYCF) indicators in a tablet-based application. We measured weight and length at birth and every three-months after that. The enumerators met precision and accuracy criteria following an anthropometry standardization procedure. Among the breastfed children, the percentage of children who achieved the minimum dietary diversity score (DDS) and minimum acceptable diet (MAD) was higher for the intervention group than

the comparison group across all age groups. The odd ratios were 3.49 (95% CI: 2.2-5.5) and 2.79 (95% CI: 1.7-4.4) for DDS and 3.49 (95% CI: 2.2-5.5) and 2.74 (95% CI: 1.8-5.2) for MAD in the 9-11 month and 16-18-month age groups, respectively. However, there was no significant improvement in growth or reduction in the prevalence of anemia. The intervention was effective in improving the feeding practices of children although it failed to show significant improvement in linear growth of children at 18 months of age.

Obesity

Oncology

(see also HIV – management of HIV related conditions)

Cancer Chemother Pharmacol. 2020 Nov;86(5):673-679.
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Efficacy and safety of oral magnesium supplementation in reducing febrile neutropenia episodes in children with solid tumors treated with cisplatin-based chemotherapy: randomized clinical trial

Osvaldo D Castelán-Martínez[1], Miguel A Palomo-Colli[2], Victoria E Barrios-López[2,3], Karla M Silva-Jivaja[4], Luis E Juárez-Villegas[2], Gilberto Castañeda-Hernández[3], Martha A Sánchez-Rodríguez[5]

Abstract

Purpose: Hypomagnesemia has been associated with febrile neutropenia (FN) in pediatric patients receiving cisplatin-based chemotherapy (CDDPBC). The primary aim was to determine whether oral magnesium supplementation reduces FN episodes in pediatric patients with solid tumors treated with CDDPBC.

Method: This randomized clinical trial, with open-label, single-center, parallel group and superiority design was conducted in Hospital Infantil de Mexico Federico Gomez at Mexico City. Children ≥ 9 years with solid tumors that were to receive a CDDPBC cycle were invited to participate. Each chemotherapy cycle with CDDPBC was randomly assigned to receive oral magnesium supplementation (250 mg/day) or not receive magnesium supplementation (control group). Efficacy was determined by relative risks (RR) with 95% confidence intervals (95% CI) as well as with numbers needed to treat (NNT). Active surveillance was conducted to assess safety in both groups. Analyses were carried out by intention to treat. ClinicalTrials.gov number NCT03449693.

Results: One hundred and one chemotherapy cycles with CDDPBC were analyzed (50 in the magnesium supplement arm and 51 in control group). Baseline clinical characteristics were similar comparing both groups. Oral magnesium supplementation reduces FN episodes compared to control group [RR 0.53, (95% CI 0.32-0.89), NNT = 4]. In the supplemented group, patients had fewer episodes of septic shock secondary to FN [RR 0.43, (95% CI 0.02-0.94), NNT = 6] and FN appeared on average 5 days later (p = 0.031). Hypomagnesemia episodes and adverse events were similar across both groups.

Conclusion: Oral supplementation with magnesium reduces FN episodes neutropenia in pediatric patients with solid tumors treated with CDDPBC.

Asian Pac J Cancer Prev. 2020 Jul 1;21(7):2117-2121.
doi: 10.31557/APJCP.2020.21.7.2117.

Efficacy Oral Glutamine to Prevent Oral Mucositis and Reduce Hospital Costs During Chemotherapy in Children with Acute Lymphoblastic Leukemia

Nur Aisiyah Widjaja[1], Ardha Pratama[1], Rendi Prihaningtyas[1], Roedi Irawan[1], Idg Ugrasena[1]

Abstract

Objective: To investigate the use of glutamine administered orally during Methotrexate chemotherapy to prevent oral mucositis and reduce hospital costs in children with acute lymphoblastic leukemia (ALL).

Methods: Twenty-four children received oral glutamine (400 mg/kg body weight per day) and twenty four received placebo on days of chemotherapy administration and for at least 14 additional days. Oral mucositis was graded daily at each day of treatment till completion of therapy. The study groups were compared for the oral mucositis development using the WHO scale.

Results: Oral mucositis occurred in 4.2 % of the glutamine group and 62.5% in the placebo group. The use of glutamine was directly associated with prevention of oral mucositis than placebo (OR 0,026; 95% CI: 0,003-0,228). The duration of length hospital stay was lower in the glutamine group than in the placebo group ((8 vs 12 days); p = 0,005). Hospital cost per day for glutamine group was 40 USD per day while placebo group was 48 USD per day.

Conclusions: There was significant difference in the prevention of oral mucositis by oral glutamine vs placebo. The hospital cost for glutamine supplementation was lower than control group.

Pediatr Blood Cancer. 2020 Sep;67(9):e28573.
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Ketamine mouthwash versus placebo in the treatment of severe oral mucositis pain in children with cancer: A randomized double-blind placebo-controlled trial

Satya Prakash[1], Jagdish Prasad Meena[1], Aditya Kumar Gupta[1], Sameer Bakhshi[2], Thirumurthy Velpandian[3], R M Pandey[4], Rachna Seth[1]

Abstract

Background and aims: Oral mucositis (OM) is a common and distressing toxicity in children on chemotherapy. There are a limited number of safe and effective therapeutic options available for OM. Ketamine oral rinse has shown promising results in a few studies in adults. This randomized, double-blind placebo-controlled trial aimed to test the efficacy of ketamine mouthwash in reducing chemotherapy-induced severe OM pain in children.

Methods: Children aged 8-18 years with severe OM were randomized to a single dose of ketamine mouthwash (4 mg/mL solution; dose 1 mg/kg) or a placebo. A sample size of 44 patients was determined. Pain score (6-point faces scale) was noted at baseline and 15, 30,

45, 60, 120, 180, and 240 min. The outcome variables were a reduction in pain score, need for rescue medications, and adverse events.
Results: The baseline characteristics were comparable in the two groups. The mean OM pain at 60 min decreased by 1.64 points (CI 1.13-2.14) in the ketamine group and 1.32 points (CI 0.76-1.87) in the placebo group (P = 0.425), with a group difference of 0.32 points. Rescue pain medication (at 60 min) was required in 13.6% in the ketamine group and 18.2% in the placebo group (P = 1.000). No significant adverse events were observed.
Conclusions: Among children on cancer chemotherapy with severe OM, ketamine mouthwash at a dose of 1 mg/kg did not significantly reduce OM pain. It did not decrease the need for rescue pain medications. Further research is warranted to test higher doses of ketamine for a clinically significant effect.

Ophthalmology, optometry and visual impairment

Cochrane Database Syst Rev. 2020 Sep 21;9:CD001862.
doi: 10.1002/14651858.CD001862.pub4.
Interventions for preventing ophthalmia neonatorum
Vimal Scott Kapoor[1], Jennifer R Evans[2], S Swaroop Vedula[3]
Abstract
Background: Ophthalmia neonatorum is an infection of the eyes in newborns that can lead to blindness, particularly if the infection is caused by Neisseria gonorrhoeae. Antiseptic or antibiotic medication is dispensed into the eyes of newborns, or dispensed systemically, soon after delivery to prevent neonatal conjunctivitis and potential vision impairment.
Objectives: 1. To determine if any type of systemic or topical eye medication is better than placebo or no prophylaxis in preventing ophthalmia neonatorum. 2. To determine if any one systemic or topical eye medication is better than any other medication in preventing ophthalmia neonatorum.
Search methods: We searched CENTRAL, MEDLINE, Embase, LILACS, and three trials registers, date of last search 4 October 2019. We also searched references of included studies and contacted pharmaceutical companies. SELECTION CRITERIA: We included randomised and quasi-randomised controlled trials of any topical, systemic, or combination medical interventions used to prevent ophthalmia neonatorum in newborns compared with placebo, no prophylaxis, or with each other.
Data collection and analysis: We used standard methods expected by Cochrane. Outcomes were: blindness or any adverse visual outcome at 12 months, conjunctivitis at 1 month (gonococcal (GC), chlamydial (CC), bacterial (BC), any aetiology (ACAE), or unknown aetiology (CUE)), and adverse effects. MAIN RESULTS: We included 30 trials with a total of 79,198 neonates. Eighteen studies were conducted in high-income settings (the USA, Europe, Israel, Canada), and 12 were conducted in low- and middle-income settings (Africa, Iran, China, Indonesia, Mexico). Fifteen of the 30 studies were quasi-randomised. We judged every study to be at high risk of bias in at least one domain. Ten studies included a comparison arm with no prophylaxis. There were 14 different prophylactic regimens and 12 different

medications in the 30 included studies. Any prophylaxis compared to no prophylaxis Unless otherwise indicated, the following evidence comes from studies assessing one or more of the following interventions: tetracycline 1%, erythromycin 0.5%, povidone-iodine 2.5%, silver nitrate 1%. None of the studies reported data on the primary outcomes: blindness or any adverse visual outcome at any time point. There was only very low-certainty evidence on the risk of GC with prophylaxis (4/5340 newborns) compared to no prophylaxis (5/2889) at one month (risk ratio (RR) 0.79, 95% confidence interval (CI) 0.24 to 2.65, 3 studies). Low-certainty evidence suggested there may be little or no difference in effect on CC (RR 0.96, 95% CI 0.57 to 1.61, 4874 newborns, 2 studies) and BC (RR 0.84, 95% CI 0.37 to 1.93, 3685 newborns, 2 studies). Moderate-certainty evidence suggested a probable reduction in risk of ACAE at one month (RR 0.65, 95% 0.54 to 0.78, 9666 newborns, 8 studies assessing tetracycline 1%, erythromycin 0.5%, povidone-iodine 2.5%, silver nitrate 1%, colostrum, bacitracin-phenacaine ointment). There was only very low-certainty evidence on CUE (RR 1.75, 95% CI 0.37 to 8.28, 330 newborns, 1 study). Very low-certainty evidence on adverse effects suggested no increased nasolacrimal duct obstruction (RR 0.93, 95% CI 0.68 to 1.28, 404 newborns, 1 study of erythromycin 0.5% and silver nitrate 1%) and no increased keratitis (single study of 40 newborns assessing silver nitrate 1% with no events). Any prophylaxis compared to another prophylaxis Overall, evidence comparing different interventions did not suggest any consistently superior intervention. However, most of this evidence was of low-certainty and was extremely limited.
Authors' conclusions: There are no data on whether prophylaxis for ophthalmia neonatorum prevents serious outcomes such as blindness or any adverse visual outcome. Moderate-certainty evidence suggests that the use of prophylaxis may lead to a reduction in the incidence of ACAE in newborns but the evidence for effect on GC, CC or BC was less certain. Comparison of individual interventions did not suggest any consistently superior intervention, but data were limited. A trial comparing tetracycline, povidone-iodine (single administration), and chloramphenicol for GC and CC could potentially provide the community with an effective, universally applicable prophylaxis against ophthalmia neonatorum.

Ophthalmic Epidemiol. 2020 Nov 30;1-9.
doi: 10.1080/09286586.2020.1851728. Online ahead of print.
Cost-minimisation Analysis from a Non-inferiority Trial of Ready-Made versus Custom-Made Spectacles for School Children in India
Neda Minakaran[1], Priya Morjaria[2], Kevin D Frick[3], Clare Gilbert[2]
Abstract
Purpose: Uncorrected refractive error is the leading cause of visual impairment in children. Many countries, including India, implement school eye health programmes involving vision screening and provision of free spectacles. This is costly for governments/organisations involved. This analysis estimates potential cost-savings if ready-made spectacles, in addition to traditional custom-made spectacles, are available for dispensing in school eye health programmes.**Methods:** An economic evaluation was conducted alongside a randomised controlled trial comparing spectacle wear of ready-made spectacles versus custom-made spectacles for children aged 11-15 years in schools in India. A cost-minimisation approach

was used to calculate cost-savings of a 'ready-made spectacles available' programme compared with a 'custom-made spectacles only' school programme. The analysis was from a service provider perspective. Main outcomes: cost-saving per child needing spectacles and cost-saving per 1000 children screened.**Results:** The prevalence of uncorrected refractive error was 2.23%, and 86% of children were eligible for ready-made spectacles. The cost per child needing spectacles in a custom-made spectacles only programme was USD$26.91, and in a ready-made spectacles available programme was $11.15, producing a 58.6% cost-saving per child needing spectacles of $15.76. Considering the total cost of the eye health programme, this equated to a 15.1% cost-saving per 1000 children screened of $361. Results were robust to multivariate sensitivity analyses.**Conclusion:** Our study is the first to demonstrate the significant cost-saving potential of ready-made spectacles in school eye health programmes for uncorrected refractive error compared with custom-made spectacles alone. This has substantial economic benefits for national/international programmes.

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doi: 10.1016/j.eclinm.2020.100594. eCollection 2020 Nov.

Effectiveness of a novel mobile health (Peek) and education intervention on spectacle wear amongst children in India: Results from a randomized superiority trial in India

Priya Morjaria[1], Andrew Bastawrous[1], Gudlavalleti Venkata Satyanarayana Murthy[1,2], Jennifer Evans[1], Mekala Jayanthi Sagar[2], Dinesh Raj Pallepogula[3], Kalluri Viswanath[4], Clare Gilbert[1]

Abstract

Background: Uncorrected refractive errors can be corrected by spectacles which improve visual functioning, academic performance and quality of life. However, spectacle wear can be low due to teasing/bullying, parental disapproval and no perceived benefit.Hypothesis: higher proportion of children with uncorrected refractive errors in the schools allocated to the intervention will wear their spectacles 3-4 months after they are dispensed.

Methods: A superiority, cluster-randomised controlled trial was undertaken in 50 government schools in Hyderabad, India using a superiority margin of 20%. Schools were the unit of randomization. Schools were randomized to intervention or a standard school programme. The same clinical procedures were followed in both arms and free spectacles were delivered to schools. Children 11-15 years with a presenting Snellen visual acuity of <6/9.5 in one or both eyes whose binocular acuity improved by ≥2 lines were recruited.In the intervention arm, classroom health education was delivered before vision screening using printed images which mimic the visual blur of uncorrected refractive error (PeekSim). Children requiring spectacles selected one image to give their parents who were also sent automated voice messages in the local language through Peek. The primary outcome was spectacle wear at 3-4 months, assessed by masked field workers at unannounced school visits. www.controlled-trials.com ISRCTN78134921 Registered on 29 June 2016.

Findings: 701 children were prescribed spectacles (intervention arm: 376, control arm: 325). 535/701 (80%) were assessed at 3-4 months: intervention arm: 291/352 (82.7%); standard arm: 244/314 (77.7%). Spectacle wear was 156/291 (53.6%) in the intervention arm and 129/244 (52.9%) in the standard arm, a difference of 0.7% (95% confidence interval (CI), -0.08,

0.09). amongst the 291 (78%) parents contacted, only 13.9% had received the child delivered PeekSim image, 70.3% received the voice messages and 97.2% understood them.
Interpretation: Spectacle wear was similar in both arms of the trial, one explanation being that health education for parents was not fully received. Health education messages to create behaviour change need to be targeted at the recipient and influencers in an appropriate, acceptable and accessible medium.

Disabil Rehabil. 2020 Jul 29;1-12.
doi: 10.1080/09638288.2020.1794063. Online ahead of print.
Multidisciplinary visual rehabilitation in low- and middle-income countries: a systematic review
Sarah Wallace[1], Rotimi Alao[2], Hannah Kuper[3], Mary Lou Jackson[4]
Abstract
Objective: To systematically review the evidence for effectiveness of rehabilitation interventions in people who are visually impaired, living in low- and middle-income countries.
Methods: Fifteen databases and the grey literature were searched up until February 2020; papers were identified according to eligibility criteria, and assessed for risk of bias. Eligible studies were controlled trials (randomised or non-randomised) of rehabilitation interventions for blind or visually impaired adults or children from low- and middle-income countries. Possible outcomes included visual acuity, activities of daily living, safety, quality of life and psychological status.
Results: Fifteen eligible studies were identified from India, Turkey, Nigeria, Croatia and Iran. Six studies were randomised, seven were non-randomised trials, and in two the method of allocation was not clear. Participants were adults, children and both adults and children. Seven studies were small ($n \leq 65$) and examined the effect of training programmes. Remaining studies compared the effect of low vision aids, economic rehabilitation, goalball, rehabilitation compliance and service delivery methods, including one large four-arm randomised trial ($n = 436$). Studies measured a variety of outcomes, and mostly showed a positive effect of interventions for pre- and post-intervention assessment, although between intervention group comparisons were often inconclusive. Overall, only four studies had a low risk of bias.
Conclusions: A lack of high-quality evidence for rehabilitation interventions is a barrier to provision of low vision services in low- and middle-income countries. Future research should focus on establishing effectiveness and cost-effectiveness of devices and models of vision rehabilitation appropriate for low-resource settings.IMPLICATIONS FOR REHABILITATIONThe systematic review found a lack of high-quality evidence for rehabilitation interventions is a barrier to provision of low vision services in low- and middle-income countries. Consider how visual rehabilitation interventions which have been shown to be effective can be delivered by non-specialists. Ensure that service providers for people who are visually impaired are trained in recognising depression and anxiety and have pathways for referral to mental health services, as appropriate.

Medicine (Baltimore). 2020 Nov 6;99(45):e22333.
doi: 10.1097/MD.0000000000022333.

Impact of rational emotive behavioral therapy on personal value system of students with visual impairment: A group randomized control study

Godwin C Abiogu[1], Moses Onyemaechi Ede[1], Fidelis E Amaeze[1], Ogechi Nnamani[1], John J Agah[2], Clifford E Ogheneakoke[3], Felix O Ugwuozor[1], Ngozi Obiyo[1], Chukwuemeka Ezurike[1], Nneka Nwosu[1], Obageli C Onyeanusi[4], Maduaka L Nweke[5], Chijioke V Amoke[1], Timothy E Asogwa[1], Emmanuel I Obeagu[6], Kelechi R Ede[7]

Abstract

Background: Visually impaired students have been reported to struggle with value system and rash decision making process. This study examined the impact of rational emotive behavioral therapy (REBT) in reducing negative personal value system of visually impaired people.

Method: A group-randomized trial design was adopted using 56 students with visual impairment. The participants received a value-based rational emotive behavior progamme and were assessed at 3 points using PVS and ABS-2-AV.

Results: The result of analysis of covariance showed that there was no significant difference between the treatment and control groups in initial personal value in Nigerian as measured by PVS. At the post-treatment the effect of V-REBP was significant in personal value and follow-up assessment respectively in favour of treatment group.

Conclusion: We concluded that there is significant impact of rational emotive behavioral therapy on reduction of negative personal value system of students with visual impairment.

Trachoma

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Targeted antibiotics for trachoma: a cluster-randomized trial

Jason S Melo[1], Solomon Aragie[2], Ambahun Chernet[2], Zerihun Tadesse[2], Adane Dagnew[2], Dagnachew Hailu[2], Mahteme Haile[3], Dionna M Wittberg[1], Scott D Nash[4], E Kelly Callahan[4], Benjamin F Arnold[1,5], Travis C Porco[1,6,5], Thomas M Lietman[1,6,5,7], Jeremy D Keenan[1,5]

Abstract

Background: Current guidelines recommend community-wide mass azithromycin for trachoma, but a targeted treatment strategy could reduce the volume of antibiotics required.

Methods: 48 Ethiopian communities were randomized to mass, targeted, or delayed azithromycin distributions. In the targeted arm, only children aged 6 months to 5 years with evidence of ocular chlamydia received azithromycin, distributed thrice over the following year. The primary outcome was ocular chlamydia at months 12 and 24, comparing the targeted and delayed arms (0-5 year-olds, superiority analysis) and the targeted and mass azithromycin arms (8-12 year-olds, non-inferiority analysis, 10% non-inferiority margin).

Results: At baseline the mean prevalence of ocular chlamydia in the three arms ranged from 7-9% among 0-5 year-olds and from 3-9% among 8-12 year-olds. Averaged across months 12-24, the mean prevalence of ocular chlamydia among 0-5 year-olds was 16.7% (95%CI 9.0%-

24.4%) in the targeted arm and 22.3% (95%CI 11.1%-33.6%) in the delayed arm (P=0.61). The final mean prevalence of ocular chlamydia among 8-12 year-olds was 13.5% (95% CI 7.9%-19.1%) in the targeted arm and 5.5% (95% CI 0.3%-10.7%) in the mass treatment arm (adjusted risk difference 8.5 percentage points [pp] higher in the targeted arm, 95% CI 0.9 pp -16.1 pp higher).
Conclusions: Antibiotic treatments targeted to infected pre-school children did not result in significantly less ocular chlamydia infections compared with untreated communities, and did not meet non-inferiority criteria relative to mass azithromycin distributions. Targeted approaches may require treatment of a broader segment of the population in areas with hyperendemic trachoma.

Oral health / dentistry

J Int Soc Prev Community Dent. 2020 Nov 24;10(6):759-765.
doi: 10.4103/jispcd.JISPCD_339_20. eCollection Nov-Dec 2020.
Plaque Removal Efficiency of Chewable Toothbrushes among 10-12-yearold Children: A Randomized Control Trial
Sridhar Nekkanti[1], Kanwardeep Kaur[2], Shwetha Balagopal[1], Priyanka Agarwal[1]
Abstract
Aim and objectives: Toothbrushing is one of the most important factors in controlling plaque accumulation and dental caries. There are vast varieties of toothbrushes available in the market. This study was designed to evaluate the effectiveness of novel chewable toothbrushes as compared to manual toothbrushes in plaque removal among 10-12-year-old children.
Materials and methods: This randomized controlled trial was conducted on 40 healthy children aged between 10 and 12 years of age who were randomly assigned to either of the groups: Group I--Chewable Toothbrushes and Group II--Manual Toothbrushes. Following oral prophylaxis, baseline records of oral hygiene indices (Simplified oral hygiene index (OHI-S) in indexed teeth and Turesky modification of Quigley Hein plaque index (TMQHI) were taken. Baseline Saliva samples were collected and sent for *Streptococcus mutans* counts. Children were then instructed to use their respective toothbrush twice daily for a week. Oral hygiene indices and *S. mutans* counts were repeated after 1 week.
Results: Differences in pre-brushing and post-brushing plaque scores and salivary *S. mutans* counts were statistically significant when compared using paired-sample *t* test and independent-sample *t* test. There was a significant reduction in salivary *S. mutans* counts after using both chewable and manual toothbrushes. However, there was no statistically significant difference between the two groups ($P = 0.08$).
Conclusion: Chewable toothbrushes are equally effective in plaque control when compared to manual toothbrushes. These can be a reliable alternative for children who lack manual dexterity.

Community Dent Oral Epidemiol. 2021 Jun;49(3):275-283.
doi: 10.1111/cdoe.12599. Epub 2020 Nov 16.

Evaluation of a community-based early childhood caries (ECC) intervention in Cambodia

Bathsheba Turton[1], Callum Durward[1], Felicity Crombie[2], Karen Sokal-Gutierrez[3], Sopharith Soeurn[1], David J Manton[4]

Abstract

Objective: To critically evaluate an early childhood caries (ECC) intervention performed by non-dental primary healthcare providers.

Methods: This mixed-methods investigation includes data from three sources: (a) a pilot non-randomized controlled trial to examine clinical outcomes at four health centres; (b) stakeholder focus group interviews; and (c) a survey of parents whose children were exposed to the intervention. The pilot study involved four Community Health Centres in rural Cambodia whereby mother-child (6-24 months of age)dyads received oral health education (OHE), toothbrushes, fluoride toothpaste and fluoride varnish on up to six occasions as part of the routine vaccination schedule. Outcomes were as follows: presence of ECC; impacts on oral health-related quality of life (OHRQoL); stakeholder perceptions of intervention delivery; and parental perceptions of fluoride varnish.

Results: Participants in the intervention group had six times lower odds of developing ECC than those in the comparison group after controlling for socio-economic status (OR 0.13). Those in the intervention group also had a large reduction OHRQoL scale scores. Key knowledge and practice gaps were identified among stakeholders. Surveyed parents had favourable views of the fluoride varnish placement by medical professionals, and four out of five stated that they would recommend fluoride varnish for other children. Primary healthcare providers, commune council representatives and community health promoters supported oral health interventions being provided in CHCs.

Conclusions: OHE and fluoride varnish interventions provided by non-dental primary health workers were feasible and acceptable for stakeholders in a Cambodian setting. The intervention group had lower ECC experience and better OHRQoL at 2 years of age.

BMC Oral Health. 2021 Jan 7;21(1):18.
doi: 10.1186/s12903-020-01374-2.

Development and evaluation of a gamified smart phone mobile health application for oral health promotion in early childhood: a randomized controlled trial

Mitra Zolfaghari[1], Mina Shirmohammadi[2,3], Houra Shahhosseini[4], Mehrshad Mokhtaran[5], Simin Z Mohebbi[6,7]

Abstract

Background: This study aimed to design a gamified smartphone application (app) and assess its efficacy for education of mothers regarding oral healthcare of their children.

Methods: In this pretest-posttest controlled clinical trial, a simple app and a gamified version of it were designed to enhance the oral health knowledge and practice of mothers. The app contains information about early childhood caries, health diet, sugars, baby-oral hygiene, fluoride effect, fluoride toothpaste, tooth-brushing training video and regular dental visits. The opinion of experts and 3 mothers were obtained and both apps were revised accordingly. The intervention was implemented on mothers of preschoolers referring to the specialty dental clinic of Tehran School of Dentistry in 2019. The mothers were

randomly allocated to the simple app or gamified app group. Before the intervention, all mothers filled out a questionnaire regarding oral health knowledge and practice, and their demographics were collected. The plaque index (PI) of children was also measured. The mothers filled out the same questionnaire 1 month after the intervention, and the PI of children was measured again. Paired t test and linear regression model were used for statistical analysis of the data.
Results: Totally, 58 mother and child pairs entered the study; 40% of children were boys. The mean age of children was 4.7 ± 1.2 years. The mean knowledge score of mothers in the pretest was 10.5 and 11.3 in simple app and gamified app group, respectively, which changed to 13.1 and 14.3, respectively in the posttest. The mean practice score of mothers was 4.4 and 4.8 in simple app and gamified app groups, respectively in the pretest, which changed to 8.5 and 8, respectively in the posttest. The mean dental plaque index of children in the pretest was 0.8 and 1 in simple app and gamified app groups, respectively, which changed to 0.5 and 0.5, respectively in the posttest. Children had better Plaque control in gamified app group ($P < 0.05$).
Conclusion: After 1 month, both apps effectively improved the oral-health knowledge and practice of mothers while oral hygiene as a result of plaque control was superior in children of mothers using the gamified app. Trial registration IRCT, IRCT20131102015238N2. Registered 24 February 2019-Retrospectively registered, https://fa.irct.ir/trial/36600 .

J Indian Soc Pedod Prev Dent. Jan-Mar 2021;39(1):95-100.
doi: 10.4103/jisppd.jisppd_465_20.
Comparison of the efficacy of parental brushing using powered versus manual tooth brush: A randomized, four-period, two-treatment, single-blinded crossover study
Pooja Mysore Purushotham[1], Arathi Rao[2], Srikant Natarajan[3], Suprabha Baranya Shrikrishna[4]
Abstract
Background: Children <5 years of age need parental assistance with tooth brushing.
Purpose: The aim is to compare the efficacy of manual and powered toothbrushes for plaque removal when used by parents to brush their children's teeth.
Methods: This randomized, four-period, two-treatment, examiner-blinded, crossover clinical trial comprised children aged 3-5 years. Tooth brushing was performed by the parent using a manual or powered toothbrush. Pre- and post-brushing plaque assessments were performed using the Turesky Modified Quigley-Hein Plaque Index. Differences in plaque scores were calculated using the paired t-test.
Results: A significant difference ($P < 0.001$) in the reduction of the plaque score was observed between the manual and powered tooth brushing groups.
Conclusion: Powered toothbrushes performed significantly better than manual toothbrushes in terms of plaque removal when used by parents to brush their child's teeth.

Poisoning and toxins

(See envenomation)

Research

Lancet Glob Health. 2021 May;9(5):e701-e710.
doi: 10.1016/S2214-109X(20)30541-6.

The role and challenges of cluster randomised trials for global health

Louis Dron[1], Monica Taljaard[2], Yin Bun Cheung[3], Rebecca Grais[4], Nathan Ford[5], Kristian Thorlund[1], Fyezah Jahan[6], Etheldreda Nakimuli-Mpungu[7], Denis Xavier[8], Zulfiqar A Bhutta[9], Jay J H Park[10], Edward J Mills[11]

Abstract

Evaluating whether an intervention works when trialled in groups of individuals can pose complex challenges for clinical research. Cluster randomised controlled trials involve the random allocation of groups or clusters of individuals to receive an intervention, and they are commonly used in global health research. In this paper, we describe the potential reasons for the increasing popularity of cluster trials in low-income and middle-income countries. We also draw on key areas of global health research for an assessment of common trial planning practices, and we address their methodological shortcomings and pitfalls. Lastly, we discuss alternative approaches for population-level intervention trials that could be useful for research undertaken in low-income and middle-income countries for situations in which the use of cluster randomisation might not be appropriate.

Lancet Glob Health. 2021 May;9(5):e691-e700.
doi: 10.1016/S2214-109X(20)30540-4.

Randomised trials at the level of the individual

Jay J H Park[1], Nathan Ford[2], Denis Xavier[3], Per Ashorn[4], Rebecca F Grais[5], Zulfiqar A Bhutta[6], Herman Goossens[7], Kristian Thorlund[8], Maria Eugenia Socias[9], Edward J Mills[10]

Abstract

In global health research, short-term, small-scale clinical trials with fixed, two-arm trial designs that generally do not allow for major changes throughout the trial are the most common study design. Building on the introductory paper of this Series, this paper discusses data-driven approaches to clinical trial research across several adaptive trial designs, as well as the master protocol framework that can help to harmonise clinical trial research efforts in global health research. We provide a general framework for more efficient trial research, and we discuss the importance of considering different study designs in the planning stage with statistical simulations. We conclude this second Series paper by discussing the methodological and operational complexity of adaptive trial designs and master protocols and the current funding challenges that could limit uptake of these approaches in global health research.

PLoS One. 2021 Mar 9;16(3):e0248263.

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Informed consent rates for neonatal randomized controlled trials in low- and lower middle-income versus high-income countries: A systematic review

Jacquelyn K Patterson[1], Stuti Pant[2], Denise F Jones[1], Syed Taha[2], Michael S Jones[3], Melissa S Bauserman[1], Paolo Montaldo[2], Carl L Bose[1], Sudhin Thayyil[2]

Abstract

Objective: Legal, ethical, and regulatory requirements of medical research uniformly call for informed consent. We aimed to characterize and compare consent rates for neonatal randomized controlled trials in low- and lower middle-income countries versus high-income countries, and to evaluate the influence of study characteristics on consent rates.

Methods: In this systematic review, we searched MEDLINE, EMBASE and Cochrane for randomized controlled trials of neonatal interventions in low- and lower middle-income countries or high-income countries published 01/01/2013 to 01/04/2018. Our primary outcome was consent rate, the proportion of eligible participants who consented amongst those approached, extracted from the article or email with the author. Using a generalised linear model for fractional dependent variables, we analysed the odds of consenting in low- and lower middle-income countries versus high-income countries across control types and interventions.

Findings: We screened 3523 articles, yielding 300 eligible randomized controlled trials with consent rates available for 135 low- and lower middle-income country trials and 65 high-income country trials. Median consent rates were higher for low- and lower middle-income countries (95.6%; interquartile range (IQR) 88.2-98.9) than high-income countries (82.7%; IQR 68.6-93.0; p<0.001). In adjusted regression analysis comparing low- and lower middle-income countries to high-income countries, the odds of consent for no placebo-drug/nutrition trials was 3.67 (95% Confidence Interval (CI) 1.87-7.19; p = 0.0002) and 6.40 (95%CI 3.32-12.34; p<0.0001) for placebo-drug/nutrition trials.

Conclusion: Neonatal randomized controlled trials in low- and lower middle-income countries report consistently higher consent rates compared to high-income country trials. Our study is limited by the overrepresentation of India among randomized controlled trials in low- and lower middle-income countries. This study raises serious concerns about the adequacy of protections for highly vulnerable populations recruited to clinical trials in low- and lower middle-income countries.

BMC Med Res Methodol. 2020 Jul 13;20(1):189.
doi: 10.1186/s12874-020-01076-x.

Quality of evidence in a post-Soviet country: evaluation of methodological quality of controlled clinical trials published in national journals from Uzbekistan

Timur Aripov[1], Dilfuza Aniyozova[2], Irina Gorbunova[3]

Abstract

Background: Most researchers in Uzbekistan prefer to publish their reports in journals of their home country. Moreover, the proportion of healthcare practitioners who prefer to use these national sources of information also remains high. However, the quality of publications from national journals, in post-Soviet countries, has not been systematically evaluated until now. The primary objective of this study was to evaluate the quality of randomized

controlled trials' (RCTs) reports published in medical journals from Uzbekistan. We supposed that reports had at least minimal quality to contribute to the higher quality of healthcare.
Methods: To evaluate the quality of RCTs, we selected two journals from the list of national medical journals for which background information was provided. We decided to select articles from journals that had the highest subscription rate and were likely to have the highest impact on clinical decisions. The journals were Medical Journal of Uzbekistan and Paediatrics. Only issues published in 2007-2017 were considered for evaluation. Two evaluators independently scored RCTs and controlled clinical trials (CCTs) reported in the journals. The 5-point scale developed by Jadad et al. was used to evaluate the quality of reports. Consensus-based decision was made about the final score of each report.
Results: We reviewed 1311 studies in the two journals and found 380 clinical trials reports for the final evaluation. Our main finding was that none of the reports received a final score of more than 1, with an absolute agreement between evaluators. A median score of the studied reports was equal to 0, predicting a very low quality of controlled trials reported in the national journals (Wilcoxon signed-rank test p = 1.0; 95% CI = 0-0).
Conclusions: We believe that quality of reports about controlled trials, in Uzbekistan, can be considered insufficient to contribute to the higher quality of care and patients' safety. In the worst case, such condition can cause serious damage to the public health and lead to ineffective use of resources in the country. Therefore, the better reporting and organization of RCTs and CCTs should become a main goal of all stakeholders interested in the effective and safe healthcare in the country.

Refugee health

Dev Psychopathol. 2021 Feb;33(1):87-95.
doi: 10.1017/S0954579419001585.
Promoting well-being in refugee children: An exploratory controlled trial of a positive psychology intervention delivered in Greek refugee camps
Sevasti Foka[1], Kristin Hadfield[1], Michael Pluess[1], Isabelle Mareschal[1]
Abstract
Rigorously evaluated interventions that target protective factors and positive resources rather than ameliorating negative outcomes in child refugees are rare. To address this, we developed and evaluated a short, group-based resilience-building intervention called Strengths for the Journey (SFJ), which was designed for war-affected children. We conducted a quasi-randomized pilot study of the SFJ intervention with 72 7- to 14-year-old forcibly displaced children (Mage = 10.76, 64.8% female) in three refugee camps in Lesvos, Greece. Intervention effectiveness was assessed by measuring pre-post changes in well-being, self-esteem, optimism, and depressive symptoms from before (T1) to immediately after the intervention/wait-list task (T2). Four focus group interviews were conducted with 31 of the participants to discuss their views on the effects of the intervention and the continued use of the skills that were learned. Using repeated-measures ANOVAs, we found improvements in well-being, F (1, 46) = 42.99, ηp2 = .48, self-esteem, F (1, 56) = 29.11, ηp2 = .40, optimism, F (1, 53) = 27.16, ηp2 = .34, and depressive symptoms, F (1, 31) = 62.14, ηp2 = .67, in the

intervention group compared with the wait-listed group ($p < .05$). Focus group participants highlighted the importance of SFJ in developing a sense of togetherness and building their strengths. Child refugees in low-resource settings may benefit from brief, first-line interventions that target protective factors such as well-being, hope, self-esteem, and belonging.

J Sch Health. 2020 Dec 2.
doi: 10.1111/josh.12979. Online ahead of print.

Social and Health Risk Factor Levels of Preschool Children Living Along the Texas-Mexico Border

Roberto Treviño-Peña[1,2], Xiaohui Wang[3], Lin Wang[2], Zasha Romero[2], Elizabeth Alanis[2], Huimin Li[3]

Abstract

Background: Childhood obesity is a public health concern that disproportionately affects populations from low socioeconomic status (SES) and minority groups. Evaluation of social and health risk factors of preschool children living along the Texas-Mexico border provides feedback to design health interventions.

Methods: South Texas Early Prevention Study-PreK (STEPS-PreK) is a cluster randomized trial designed to assess the effect of the Bienestar coordinated school health program on children's health outcomes. Family characteristics, dietary intake, fitness, and anthropometric data were collected from 1277 preschool students enrolled in 28 preschools.

Results: The response rate was 67%. Overall, 57% of families lived in poverty. The mean age of students was 4.7 years, 95% were Hispanic, and 51% were male. The average serving of fruits and vegetables per day were 1 and 1/3, respectively. Of these, students consumed 39.7% of fruits and 18.9% of vegetables. Obesity prevalence for boys was 19.2% and for girls 16.8%. Nearly one-half reported some form of food insecurity.

Conclusions: Children living in low-income areas are affected by high levels of social and health risk factors. It is these families who should be targeted with early-age and culturally appropriate health programs.

Int J Environ Res Public Health. 2020 Nov 20;17(22):8627.
doi: 10.3390/ijerph17228627.

Global Mental Health and Services for Migrants in Primary Care Settings in High-Income Countries: A Scoping Review

Jia Lu[1], Shabana Jamani[2], Joseph Benjamen[2], Eric Agbata[3], Olivia Magwood[3,4], Kevin Pottie[3,5]

Abstract

Migrants are at a higher risk for common mental health problems than the general population but are less likely to seek care. To improve access, the World Health Organization (WHO) recommends the integration of mental health services into primary care. This scoping review aims to provide an overview of the types and characteristics of mental health services provided to migrants in primary care following resettlement in high-income countries. We systematically searched MEDLINE, EMBASE, PsycInfo, Global Health, and other databases from 1 January 2000 to 15 April 2020. The inclusion criteria consisted of all studies published in English, reporting mental health services and practices for refugee, asylum seeker, or

undocumented migrant populations, and were conducted in primary care following resettlement in high-income countries. The search identified 1627 citations and we included 19 studies. The majority of the included studies were conducted in North America. Two randomized controlled trials (RCTs) assessed technology-assisted mental health screening, and one assessed integrating intensive psychotherapy and case management in primary care. There was a paucity of studies considering gender, children, seniors, and in European settings. More equity-focused research is required to improve primary mental health care in the context of global mental health.

Schistosomiasis

PLoS Negl Trop Dis. 2020 Sep 23;14(9):e0008619.
doi: 10.1371/journal.pntd.0008619. eCollection 2020 Sep.

Efficacy and safety of praziquantel and dihydroartemisinin piperaquine combination for treatment and control of intestinal schistosomiasis: A randomized, non-inferiority clinical trial

Rajabu Hussein Mnkugwe[1,2], Omary Minzi[3], Safari Kinung'hi[4], Appolinary Kamuhabwa[3], Eleni Aklillu[2]

Abstract

Background: Despite the reported success in reducing morbidity, praziquantel alone is insufficient for the control and elimination of schistosomiasis, partly due to its poor efficacy against the juvenile worms. Artemisinin derivatives are effective against juvenile worms but are less effective against adult worms. We compared the safety and efficacy of praziquantel and Dihydroartemisinin-piperaquine combination against the standard praziquantel alone for treatment of intestinal schistosomiasis.

Methods: In this randomized, open-label, non-inferiority trial, 639 Schistosoma mansoni infected children were enrolled and randomized to receive either praziquantel alone or praziquantel plus Dihydroartemisinin-piperaquine combination. Two stool samples were collected on consecutive days at baseline, 3 and 8 weeks post-treatment and analyzed using thick smear Kato Katz method. Efficacy was assessed by cure and egg reduction rates at 3 and 8 weeks post-treatment. Adverse events were assessed within four hours of drugs intake. The primary outcome was cure rates at 8 weeks of post-treatment. Secondary outcomes were egg reduction rates at 8 weeks of post-treatment and treatment-associated adverse events.

Results: At 3 weeks of post-treatment, cure rates were 88.3% (263/298, 95% CI = 84.1%- 91.4%) and 81.2% (277/341, 95% CI = 76.7%- 85.0%) for the combination therapy and praziquantel alone, respectively ($p < 0.01$, odds ratio (OR) = 1.74, 95% CI of OR = 1.11 to 2.69). At 8 weeks, there was a significant drop in the cure rates in praziquantel alone group to 63.9% (218/341, 95% CI = 58.7%- 68.8%) compared to 81.9% (244/298, 95% CI = 77.1%- 85.8%) in the combination therapy group ($p < 0.0001$, OR = 2.55, 95%CI of OR = 1.75 to 3.69). Egg reduction rates at 8 weeks post-treatment were significantly higher in the combination therapy group 93.6% (95% CI = 90.8%- 96.4%) compared to 87.9% (95% CI = 84.4%- 91.4%) in the praziquantel only group ($p = 0.01$). On both Univariate and Multivariate regression analysis, type of treatment received was a significant predictor of cure at week 8 post-

treatment. Overall, 30.8% (95% CI = 27.2%- 34.4%) of the study participants experienced mild and transient treatment-associated adverse events, post-treatment abdominal pain (27.1%) being the most common adverse event observed. There was no significant difference in the overall occurrence of adverse events between the two treatment groups.
Conclusion: Praziquantel and Dihydroartemisinin piperaquine combination therapy is safe, and more efficacious compared to praziquantel alone for the treatment of intestinal schistosomiasis. Further studies are needed to explore if the combination therapy can be considered as an option for mass drug administration to control and eventually eliminate schistosomiasis.

S Afr Med J. 2020 Jul 7;110(7):657-660.
doi: 10.7196/SAMJ.2020.v110i7.13926.

Comparison of praziquantel efficacy at 40 mg/kg and 60 mg/kg in treating Schistosoma haematobium infection among schoolchildren in the Ingwavuma area, KwaZulu-Natal, South Africa

M Kabuyaya[1], M J Chimbari, S Mukaratirwa

Abstract
Background: The World Health Organization recommends praziquantel (PZQ) (40 mg/kg body weight) for treating schistosomiasis. However, drug failure has been reported, prompting use of 60 mg/kg, for which results have been inconsistent.
Objectives: To compare the efficacy of PZQ 40 mg/kg and 60 mg/kg in treating schoolchildren infected with Schistosoma haematobium.
Methods: The study was conducted during November 2017 - August 2018 in the Ingwavuma area, uMkhanyakude District, KwaZulu-Natal Province, South Africa. Children aged 10 - 15 years were screened for S. haematobium using a filtration technique. Infected children were randomly assigned to a dose of PZQ of 40 mg/kg or 60 mg/kg. Side-effects were recorded within 24 hours after treatment using questionnaires and direct observation. Four weeks after treatment, participants were retested for S. haematobium infection. Baseline and post-treatment mean egg counts were calculated. Cure rate (CR) and egg reduction rate (ERR) were used to determine PZQ efficacy, while repeated-measures analysis of variance determined the effect of both doses on infection intensity. A $\chi 2$ test was used to determine the association of side-effects with treatment, with a p-value ≤0.05.
Results: Forty-three and 36 children were treated with PZQ 40 mg/kg and 60 mg/kg, respectively. The 40 mg/kg group had a CR of 79.0% and an ERR of 97.2%, and the 60 mg/kg group a CR of 83.0% and an ERR of 98.3%. The effect of dose on infection intensity was not significantly different between the two groups ($p<0.05$). Abdominal pains, dizziness and fatigue were common among children who received PZQ 40 mg/kg, while headache, dizziness and nausea were common in the 60 mg/kg group.
Conclusions: The efficacy of PZQ at 60 mg/kg was similar to that at 40 mg/kg. A dose >40 mg/kg therefore does not add value in treating S. haematobium infection. Transient side-effects (mostly dizziness) were observed more in the 60 mg/kg group than in the 40 mg/kg group. We recommend continued use of 40 mg/kg body weight for treating schistosomiasis.

Acta Trop. 2021 Aug;220:105960.
doi: 10.1016/j.actatropica.2021.105960. Epub 2021 May 15.

Evaluation of a urogenital schistosomiasis behavioural intervention among students from rural schools in Unguja and Pemba islands, Zanzibar

Bobbie Person[1], David Rollinson[2], Said M Ali[3], Ulfat A Mohammed[3], Faiza M A'kadir[4], Fatma Kabole[4], Stefanie Knopp[5]

Abstract

Urogenital schistosomiasis is a common experience among children in Zanzibar. There is a paucity of behavioural science-based, health education and behaviour change (HEBC) interventions for school-aged children, those at greatest risk for urogenital schistosomiasis. We assessed the influence of a HEBC intervention, guided by the Health Belief model, among rural schoolchildren on Pemba and Unguja islands in Zanzibar, Tanzania. From 2012 to 2016, a cluster-randomized trial to assess three different interventions against urogenital schistosomiasis was conducted in 90 schools and shehias across Zanzibar. The HEBC intervention was implemented in 15 schools per island. In 2017, at the trial conclusion, we administered written questionnaires to schoolchildren from 4 HEBC intervention schools and 4 not HEBC exposed schools on each island, respectively. Responses were compared between students that were exposed or not exposed to the HEBC intervention using a Fisher's exact test. A total of 1451 students, 708 from intervention and 743 from non-intervention schools completed the questionnaire. Noting some between island differences, students who had received the HEBC interventions reported significant improvements in knowledge about Schistosoma haematobium transmission and personal risk, strategies for schistosomiasis prevention, and self-reported changes in risk behaviours: stopped washing laundry/dishes 49.4% (350/708) versus 5.8% (43/743), stopped bathing in streams/ponds 49.4% (350/708) versus 4.2% (31/743), and stopped playing in streams/ponds 40.8% (289/708) versus 10.8% (80/743). HEBC exposed children also reported a significant increase in swallowing tablets during mass drug administration (MDA) campaigns (when they had not before) 30.2% (214/708) versus 4.6% (34/743). The school based HEBC interventions were associated with desirable positive behaviour change among students. Data suggest that scaling up HEBC interventions to all schools in high-risk areas, augmented with bi-annual MDA, can help to reduce prevalence of urogenital schistosomiasis in Zanzibar, strengthening the possibility for future disease elimination.

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Impact of Different Mass Drug Administration Strategies for Gaining and Sustaining Control of *Schistosoma mansoni* and *Schistosoma haematobium* Infection in Africa

Charles H King[1,2], Nupur Kittur[2], Sue Binder[2], Carl H Campbell[2], Eliézer K N'Goran[3,4], Aboulaye Meite[5], Jürg Utzinger[6,7], Annette Olsen[8], Pascal Magnussen[9], Safari Kinung'hi[10], Alan Fenwick[11], Anna E Phillips[11], Pedro H Gazzinelli-Guimaraes[11], Neerav Dhanani[11], Josefo Ferro[12], Diana M S Karanja[13], Pauline N M Mwinzi[13], Susan P Montgomery[14], Ryan E Wiegand[14,6,7], William Evan Secor[14], Amina A Hamidou[15], Amadou Garba[16], Daniel G Colley[17,2]

Abstract

This report summarizes the design and outcomes of randomized controlled operational research trials performed by the Bill & Melinda Gates Foundation-funded Schistosomiasis

Consortium for Operational Research and Evaluation (SCORE) from 2009 to 2019. Their goal was to define the effectiveness and test the limitations of current WHO-recommended schistosomiasis control protocols by performing large-scale pragmatic trials to compare the impact of different schedules and coverage regimens of praziquantel mass drug administration (MDA). Although there were limitations to study designs and performance, analysis of their primary outcomes confirmed that all tested regimens of praziquantel MDA significantly reduced local *Schistosoma* infection prevalence and intensity among school-age children. Secondary analysis suggested that outcomes in locations receiving four annual rounds of MDA were better than those in communities that had treatment holiday years, in which no praziquantel MDA was given. Statistical significance of differences was obscured by a wider-than-expected variation in community-level responses to MDA, defining a persistent hot spot obstacle to MDA success. No MDA schedule led to elimination of infection, even in those communities that started at low prevalence of infection, and it is likely that programs aiming for elimination of transmission will need to add supplemental interventions (e.g., snail control, improvement in water, sanitation and hygiene, and behavior change interventions) to achieve that next stage of control. Recommendations for future implementation research, including exploration of the value of earlier program impact assessment combined with intensification of intervention in hot spot locations, are discussed.

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Effectiveness of school-based preventive chemotherapy strategies for sustaining the control of schistosomiasis in Côte d'Ivoire: Results of a 5-year cluster randomized trial

Mamadou Ouattara[1,2], Nana R Diakité[1,2], Patrick K Yao[1], Jasmina Saric[3,4], Jean T Coulibaly[1,2,3,4], Rufin K Assaré[1,2,3,4], Fidèle K Bassa[1,2], Naférima Koné[1], Négnorogo Guindo-Coulibaly[1], Jan Hattendorf[3,4], Jürg Utzinger[3,4], Eliézer K N'Goran[1,2]

Abstract

Background: Preventive chemotherapy using praziquantel is the mainstay for schistosomiasis control. However, there is little evidence on what is supposed to be the most effective school-based treatment strategy to sustain morbidity control. The aim of this study was to compare differences in Schistosoma mansoni prevalence and infection intensity between three different schedules of school-based preventive chemotherapy in an area with moderate prevalence of S. mansoni in Côte d'Ivoire.

Methodology: Seventy-five schools were randomly assigned to one of three intervention arms: (i) annual school-based preventive chemotherapy with praziquantel (40 mg/kg) over four years; (ii) praziquantel treatment only in the first two years, followed by two years whithout treatment; and (iii) praziquantel treatment in years 1 and 3 without treatment in-between. Cross-sectional parasitologic surveys were carried out prior to each round of preventive chemotherapy. The difference in S. mansoni prevalence and infection intensity was assessed by multiple Kato-Katz thick smears, among children aged 9-12 years at the time of each survey. First-grade children, aged 5-8 years who had never received praziquantel, were also tested at baseline and at the end of the study.

Principal findings: Overall, 7,410 children aged 9-12 years were examined at baseline and 7,223 at the final survey. The baseline prevalence of S. mansoni was 17.4%, 20.2%, and 25.2%

in arms 1, 2, and 3, respectively. In the final year, we observed the lowest prevalence of 10.4% in arm 1, compared to 18.2% in arm 2 and 17.5% in arm 3. The comparison between arms 1 and 2 estimated an odds ratio (OR) of 0.52 but the difference was not statistically significant (95% confidence interval (CI) = 0.23-1.16). Likewise the difference between arms 1 and 3 lacked statistical significance (OR = 0.55, 95% CI = 0.23-1.29). There was no noteworthy difference observed between arms 2 and 3 (OR = 1.06, 95% CI = 0.64-1.75). The lowest S. mansoni fecal egg counts in the final year survey were observed in arm 1 (7.9 eggs per gram of stool (EPG)). However, compared with 11.5 EPG in arm 2 and 15.4 EPG in arm 3, the difference lacked statistical significance. There were 4,812 first-grade children examined at baseline and 4,513 in the final survey. The overall prevalence of S. mansoni in these children slightly decreased in arms 1 (from 4.5% to 3.6%) and 2 (from 4.7% to 4.3%), but increased in arm 3 (from 6.8% to 7.9%). However, there was no significant difference in prevalence and infection intensity observed between study arms.
Conclusions/significance: The three treatment schedules investigated led to a reduction in the prevalence and intensity of S. mansoni infection among children aged 9-12 years. Comparing intervention arms at the end of the study, no statistically significant differences were observed between annual treatement and the other two treatment schedules, neither in reduction of prevalence nor intensity of infection. It is important to combine our results with those of three sister trials conducted simultaneously in other African countries, before final recommendations can be drawn.

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SCORE Operational Research on Moving toward Interruption of Schistosomiasis Transmission

Carl H Campbell[1], Sue Binder[1], Charles H King[2 1], Stefanie Knopp[3 4 5], David Rollinson[6 3], Bobbie Person[1], Bonnie Webster[6 3], Fiona Allan[6 3], Jürg Utzinger[4 5], Shaali M Ame[7], Said M Ali[7], Fatma Kabole[8], Eliézer K N'Goran[9 10], Fabrizio Tediosi[4 5], Paola Salari[4 5], Mamadou Ouattara[9 10], Nana R Diakité[9 10], Jan Hattendorf[4 5], Tamara S Andros[1], Nupur Kittur[1], Daniel G Colley[11 1]

Abstract
As part of its diverse portfolio, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) included two cluster-randomized trials evaluating interventions that could potentially lead to interruption of schistosomiasis transmission (elimination) in areas of Africa with low prevalence and intensity of infection. These studies, conducted in Zanzibar and Côte d'Ivoire, demonstrated that multiyear mass drug administration (MDA) with praziquantel failed to interrupt the transmission of urogenital schistosomiasis, even when provided biannually and/or supplemented by small-scale implementation of additional interventions. Other SCORE activities related to elimination included a feasibility and acceptability assessment of test-treat-track-test-treat (T5) strategies and mathematical modeling. Future evaluations of interventions to eliminate schistosomiasis should recognize the difficulties inherent in conducting randomized controlled trials on elimination and in

measuring small changes where baseline prevalence is low. Highly sensitive and specific diagnostic tests for use in very low-prevalence areas for schistosomiasis are not routinely available, which complicates accurate measurement of infection rates and assessment of changes resulting from interventions in these settings. Although not encountered in these two studies, as prevalence and intensity decrease, political and community commitment to population-wide MDA may decrease. Because of this potential problem, SCORE developed and funded the T5 strategy implemented in Egypt, Kenya, and Tanzania. It is likely that focal MDA campaigns, along with more targeted approaches, including a T5 strategy and snail control, will need to be supplemented with the provision of clean water and sanitation and behavior change communications to achieve interruption of schistosome transmission.

School health and education

(See Adolescent health, Schistosomiasis)

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Right To Play's intervention to reduce peer violence among children in public schools in Pakistan: a cluster-randomized controlled trial

Rozina Karmaliani[1], Judith McFarlane[2], Hussain Maqbool Ahmed Khuwaja[1], Yasmeen Somani[1], Shireen Shehzad[1], Tazeen Saeed Ali[1], Nargis Asad[3], Esnat D Chirwa[4 5], Rachel Jewkes[4]

Abstract

Background: Peer violence is common globally, but a little researched topic in low-and middle-income countries. This study presents the evaluation of a two-year randomized controlled trial of a structured play-based life-skills intervention implemented in schools in Hyderabad, Pakistan.

Objective: To determine the impact of the intervention on school-based peer violence (victimization and perpetration) and depression among school children.

Methods: 40 single-sex public schools were randomized into two study arms (20 per arm 10 of each sex). A total of 1752 grade 6 students (929 from intervention and 823 from control schools) were enrolled in the trial. The two-year intervention was a biweekly structured game led by a coach followed by critical reflection and discussion for 30 minutes. Primary outcomes (exposure to peer violence exhibited through victimization and perpetration and depression) were evaluated using generalized linear-mixed models.

Results: Of the enrolled children (N = 1752) 91% provided data for analysis. There were significant decreases in self-reported peer violence victimization, perpetration and depression. For peer violence victimization, the reductions in the intervention and control arms were: 33.3% versus 27.8% for boys and 58.5% versus 21.3% for girls. For peer violence perpetration, the reductions were: 25.3% versus 11.1% for boys and 55.6% versus 27.6% for girls in the intervention and control arms, respectively. There were significant drops in mean depression scores (boys 7.2% versus 4.8% intervention and control and girls 9.5% versus 5.6% intervention and control).

Conclusion: A well-designed and implemented play-based life-skills intervention delivered in public schools in Pakistan is able to effect a significant reduction in peer violence.

Public Health Nutr. 2020 Oct;23(14):2626-2636.
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Effectiveness of school-based nutrition interventions in sub-Saharan Africa: a systematic review

Paul Kyere[1], J Lennert Veerman[1], Patricia Lee[1], Donald E Stewart[1]

Abstract

Objective: To evaluate the effect of school-based nutrition interventions (SBNI) involving schoolchildren and adolescents in sub-Saharan Africa (SSA) on child nutrition status and nutrition-related knowledge, attitudes and behaviour.

Design: A systematic review on published school nutrition intervention studies of randomised controlled trials, controlled clinical trials, controlled before-and-after studies or quasi-experimental designs with control. Nine electronic bibliographic databases were searched. To be included, interventions had to involve changes to the school's physical and social environments, to the school's nutrition policies, to teaching curriculum to incorporate nutrition education and/or to partnership with parents/community.

Setting: Schools in SSA.

Participants: School-aged children and adolescents, aged 5-19 years.

Results: Fourteen studies met our inclusion criteria. While there are few existing studies of SBNI in SSA, the evidence shows that food supplementation/fortification is very effective in reducing micronutrient deficiencies and can improve nutrition status. Secondly, school nutrition education can improve nutrition knowledge, but this may not necessarily translate into healthy nutrition behaviour, indicating that nutrition knowledge may have little impact without a facilitating environment. Results regarding anthropometry were inconclusive; however, there is evidence for the effectiveness of SBNI in improving cognitive abilities.

Conclusions: There is enough evidence to warrant further trials of SBNI in SSA. Future research should consider investigating the impact of SBNI on anthropometry and nutrition behaviour, focusing on the role of programme intensity and/or duration. To address the high incidence of micronutrient deficiencies in low- and middle-income countries, food supplementation strategies currently available to schoolchildren should be expanded.

Sepsis and serious bacterial infection

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Costs and cost-effectiveness of management of possible serious bacterial infections in young infants in outpatient settings when referral to a hospital was not possible: Results from randomized trials in Africa

Charu C Garg[1], Antoinette Tshefu[2], Adrien Lokangaka Longombe[2], Jean-Serge Ngaima Kila[2], Fabian Esamai[3], Peter Gisore[3], Adejumoke Idowu Ayede[4], Adegoke Gbadegesin Falade[4], Ebunoluwa A Adejuyigbe[5], Chineme Henry Anyabolu[5], Robinson D Wammanda[6], Joshua Daba Hyellashelni[6], Sachiyo Yoshida[7], Lu Gram[8], Yasir Bin Nisar[7], Shamim Ahmad Qazi[1], Rajiv Bahl[7]

Abstract

Introduction: Serious bacterial neonatal infections are a major cause of global neonatal mortality. While hospitalized treatment is recommended, families cannot access inpatient treatment in low resource settings. Two parallel randomized control trials were conducted at five sites in three countries (Democratic Republic of Congo, Kenya, and Nigeria) to compare the effectiveness of treatment with experimental regimens requiring fewer injections with a reference regimen A (injection gentamicin plus injection procaine penicillin both once daily for 7 days) on the outpatient basis provided to young infants (0-59 days) with signs of possible serious bacterial infection (PSBI) when the referral was not feasible. Costs were estimated to quantify the financial implications of scaleup, and cost-effectiveness of these regimens.

Methods: Direct economic costs (including personnel, drugs and consumable costs) were estimated for identification, prenatal and postnatal visits, assessment, classification, treatment and follow-up. Data on time spent by providers on each activity was collected from 83% of providers. Indirect marginal financial costs were estimated for non-consumables/capital, training, transport, communication, administration and supervision by considering only a share of the total research and health system costs considered important for the program. Total economic costs (direct plus indirect) per young infant treated were estimated based on 39% of young infants enrolled in the trial during 2012 and the number of days each treated during one year. The incremental cost-effectiveness ratio was calculated using treatment failure after one week as the outcome indicator. Experimental regimens were compared to the reference regimen and pairwise comparisons were also made.

Results: The average costs of treating a young infant with clinical severe infection (a sub-category of PSBI) in 2012 was lowest with regimen D (injection gentamicin once daily for 2 days plus oral amoxicillin twice daily for 7 days) at US$ 20.9 (95% CI US$ 16.4-25.3) or US$ 32.5 (2018 prices). While all experimental regimens B (injection gentamicin once daily plus oral amoxicillin twice daily, both for 7 days), regimen C (once daily of injection gentamicin injection plus injection procaine penicillin for 2 days, thereafter oral amoxicillin twice daily for 5 days) and regimen D were found to be more cost-effective as compared with the reference regimen A; pairwise comparison showed regimen D was more cost-effective than B or C. For fast breathing, the average cost of treatment with regimen E (oral amoxicillin twice daily for 7 days) at US$ 18.3 (95% CI US$ 13.4-23.3) or US$ 29.0 (2018 prices) was more cost-effective than regimen A. Indirect costs were 32% of the total treatment costs.

Conclusion: Scaling up of outpatient treatment for PSBI when the referral is not feasible with fewer injections and oral antibiotics is cost-effective for young infants and can lead to increased access to treatment resulting in potential reductions in neonatal mortality.

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doi: 10.1186/s13613-021-00822-8.

Validation of the pediatric refractory septic shock definition: post hoc analysis of a controlled trial

Luc Morin[#1], Karthik Narayanan Ramaswamy[#2], Muralidharan Jayashree[2], Arun Bansal[2], Karthi Nallasamy[2], Pierre Tissieres[3 4], Sunit Singhi[2]

Abstract

Background: The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) developed and validated a definition of pediatric refractory septic shock (RSS), based on two septic shock scores (SSS). Both bedside SSS (bSSS) and computed SSS (cSSS) were found to be strongly associated with mortality. We aimed at assessing the accuracy of the RSS definition on a prospective cohort from India.

Methods: Post hoc analysis of a cohort issued from a double-blind randomized trial that compared first-line vasoactive drugs in children with septic shock. Sequential bSSS and cSSS from 60 children (single-center study, 53% mortality) were analyzed. The prognostic value of the ESPNIC RSS definition was tested for 28-day all-cause mortality.

Results: In this septic shock cohort, RSS was diagnosed in 35 patients (58.3%) during the first 24 h. Death occurred in 30 RSS patients (85.7% mortality) and in 2 non-RSS patients (8% mortality), OR = 60.9 [95% CI: 10.5-676.2], $p < 0.001$ with a median delay from sepsis onset of 3 days [1.0-6.7]. Among patients diagnosed with RSS, the mortality was not significantly different according to vasopressors randomization. Diagnosis of RSS with bSSS and cSSS had a high discrimination for death with an area under the receiver operating curve of 0.916 [95% CI: 0.843-0.990] and 0.925 [95% CI: 0.845-1.000], respectively. High prognostic accuracy of the bSSS was found in the first hours following intensive care admission. The best interval of prognostication occurs after the 12th hour following treatment initiation (AUC 0.973 [95% CI: 0.925-1.000]).

Conclusions: The ESPNIC refractory septic shock definition accurately identifies, within the first 6 h of septic shock management, children with lethal outcome.

Skin disease

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Emerging Treatment Strategies for Impetigo in Endemic and Nonendemic Settings: A Systematic Review

Garima Gahlawat[1], Wubshet Tesfaye[1], Mary Bushell[1], Solomon Abrha[2], Gregory M Peterson[3], Cynthia Mathew[1], Mahipal Sinnollareddy[4], Faye McMillan[5], Indira Samarawickrema[1], Tom Calma[1], Aileen Y Chang[6], Daniel Engelman[7], Andrew Steer[7], Jackson Thomas[8]

Abstract

Purpose: Impetigo affects approximately 162 million children worldwide at any given time. Lack of consensus on the most effective treatment strategy for impetigo and increasing antibiotic resistance continue to drive research into newer and alternative treatment

options. We conducted a systematic review to assess the effectiveness of new treatments for impetigo in endemic and nonendemic settings.
Methods: We searched PubMed, MEDLINE, CINAHL, Web of Science, and Embase via Scopus for studies that explored treatments for bullous, nonbullous, primary, and secondary impetigo published between August 1, 2011, and February 29, 2020. We also searched online trial registries and hand-searched the reference lists of the included studies. We used the revised Cochrane risk of bias (version 2.0) tool for randomized trials and the National Heart, Lung, and Blood Institute for nonrandomized uncontrolled studies to assess the risk of bias.
Findings: We included 10 studies that involved 6651 participants and reported on 9 treatments in the final analysis. Most clinical trials targeted nonbullous impetigo or did not specify this. The risk of bias varied among the studies. In nonendemic settings, ozenoxacin 1% cream appeared to have the strongest evidence base compared with retapamulin and a new minocycline formulation. In endemic settings, oral co-trimoxazole and benzathine benzylpenicillin G injection were equally effective in the treatment of severe impetigo. Mass drug administration intervention emerged as a promising public health strategy to reduce the prevalence of impetigo in endemic settings.
Implications: This review highlights the limited research into new drugs used for the treatment of impetigo in endemic and nonendemic settings. Limited recent evidence supports the use of topical ozenoxacin or retapamulin for impetigo treatment in nonendemic settings, whereas systemic antibiotics and the mass drug administration strategy have evidence for use in endemic settings. Given the troubling increase in resistance to existing treatments, there is a clear need to ensure the judicious use of antibiotics and to develop new treatments and alternative strategies; this is particularly important in endemic settings

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A comparative study of the efficacy and safety of intralesional measles, mumps, and rubella vaccine versus intralesional vitamin D3 for the treatment of warts in children

Alpana Mohta[1], Ramesh Kumar Kushwaha[1], Umesh Gautam[1], Pritee Sharma[1], Asha Nyati[1], Suresh Kumar Jain[1]

Abstract
Background: Intralesional vitamin D3 has recently emerged as a new treatment for cutaneous warts. The use of the measles, mumps, and rubella (MMR) vaccine for this purpose is an established modality. However, relevant data on the efficacy of either the MMR vaccine or vitamin D3 as immunotherapy for cutaneous warts in the pediatric population are limited.
Objectives: To compare the efficacy and safety of intralesional injections of MMR vaccine to intralesional injections of vitamin D3 in children aged 8-16 years with multiple warts.
Methods: A total of 74 children were randomly allocated into two groups. Group A patients received intralesional MMR vaccine into the largest wart, and group B received intralesional vitamin D3 into the largest wart. The injections were repeated every 4 weeks until clearance or for a maximum of three treatments. After the last injection, children were followed up every 2 weeks for 3 months, and at the sixth month, a final clinical assessment was conducted.

Results: Of 74 children, 60 completed the study, with 30 children in each group. Complete clearance of the injected wart was observed in 26 (86.67%) patients in the MMR group (group A) and 23 (76.7%) patients in the vitamin D3 group (group B). Distant warts cleared in 23 (76.7%) patients in group A compared to 20 (66.6%) patients in group B. There was no significant difference between groups. No recurrence was seen in group A, whereas two (6.6%) children in group B exhibited recurrence in the ensuing 6-month follow-up. The most common adverse events were injection site pain and swelling.
Conclusion: Both intralesional MMR and vitamin D3 are safe, generally well-tolerated, and equally effective in children for the treatment of cutaneous warts.

Snake bite and envenomation

Surgical problems

Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

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Community-based active case-finding interventions for tuberculosis: a systematic review
Rachael M Burke[1], Marriott Nliwasa[2], Helena R A Feasey[3], Lelia H Chaisson[4], Jonathan E Golub[5], Fahd Naufal[5], Adrienne E Shapiro[6], Maria Ruperez[7], Lily Telisinghe[8], Helen Ayles[8], Elizabeth L Corbett[3], Peter MacPherson[9]
Abstract
Background: Community-based active case-finding interventions might identify and treat more people with tuberculosis disease than standard case detection. We aimed to assess whether active case-finding interventions can affect tuberculosis epidemiology in the wider community.
Methods: We did a systematic review by searching PubMed, Embase, Scopus, and Cochrane Library for studies that compared tuberculosis case notification rates, tuberculosis disease prevalence, or tuberculosis infection prevalence or incidence in children, between populations exposed and unexposed to active case-finding interventions. We included studies published in English between Jan 1, 1980, and April 13, 2020. Studies of active case-finding in the general population, in populations perceived to be at high risk for tuberculosis, and in closed settings were included, whereas studies of tuberculosis screening at health-care facilities, among household contacts, or among children only, and studies that screened fewer than 1000 people were excluded. To estimate effectiveness, we extracted or calculated case notification rates, prevalence of tuberculosis disease, and incidence or prevalence of tuberculosis infection in children, and compared ratios of these outcomes between groups that were exposed or not exposed to active case-finding interventions.

Results: 27 883 abstracts were screened and 988 articles underwent full text review. 28 studies contributed data for analysis of tuberculosis case notifications, nine for prevalence of tuberculosis disease, and two for incidence or prevalence of tuberculosis infection in children. In one cluster-randomised trial in South Africa and Zambia, an active case-finding intervention based on community mobilisation and sputum drop-off did not affect tuberculosis prevalence, whereas, in a cluster-randomised trial in Vietnam, an active case-finding intervention based on sputum tuberculosis tests for everyone reduced tuberculosis prevalence in the community. We found inconsistent, low-quality evidence that active case-finding might increase the number of cases of tuberculosis notified in populations with structural risk factors for tuberculosis.
Interpretation: Community-based active case-finding for tuberculosis might be effective in changing tuberculosis epidemiology and thereby improving population health if delivered with high coverage and intensity. If possible, active case-finding projects should incorporate a well designed, robust evaluation to contribute to the evidence base and help elucidate which delivery methods and diagnostic strategies are most effective.

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Accuracy of Xpert Ultra in Diagnosis of Pulmonary Tuberculosis among Children in Uganda: a Substudy from the SHINE Trial

Willy Ssengooba[1,2], Jean de Dieu Iragena[3], Lydia Nakiyingi[4], Serestine Mujumbi[5], Eric Wobudeya[6], Robert Mboizi[6], David Boulware[4], David B Meya[4], Louise Choo[7], Angela M Crook[7], Kristen Lebeau[7], Moses Joloba[5], Anne-Marie Demers[8], Fiona V Cresswell[6,9,10], Diana M Gibb[7]

Abstract
Childhood tuberculosis (TB) presents significant diagnostic challenges associated with paucibacillary disease and requires a more sensitive test. We evaluated the diagnostic accuracy of Xpert MTB/RIF Ultra (Ultra) compared to other microbiological tests using respiratory samples from Ugandan children in the SHINE trial. SHINE is a randomized trial evaluating shorter treatment in 1,204 children with minimal TB disease in Africa and India. Among 352 samples and one cervical lymph node fine needle aspirate, one sample was randomly selected per patient and tested with the Xpert MTB/RIF assay (Xpert) and with Lowenstein-Jensen medium (LJ) and liquid mycobacterial growth indicator tube (MGIT) cultures. We selected only uncontaminated stored sample pellets for Ultra testing. We estimated the sensitivity of Xpert and Ultra against culture and a composite microbiological reference standard (any positive result). Of 398 children, 353 (89%) had culture, Xpert, and Ultra results. The median age was 2.8 years (interquartile range [IQR], 1.3 to 5.3); 8.5% (30/353) were HIV infected, and 54.4% (192/353) were male. Of the 353, 31 (9%) were positive by LJ and/or MGIT culture, 36 (10%) by Ultra, and 16 (5%) by Xpert. Sensitivities (95% confidence intervals [CI]) were 58% (39 to 65% [18/31]) for Ultra and 45% (27 to 64% [14/31]) for Xpert against any culture-positive result, with false positives of <1% and 5.5% for Xpert and Ultra. Against a composite microbiological reference, sensitivities were 72% (58 to 84% [36/50]) for Ultra and 32% (20 to 47% [16/50]) for Xpert. However, there were 17 samples that were positive only with Ultra (majority trace). Among children screened for minimal TB in

Uganda, Ultra has higher sensitivity than Xpert. This represents an important advance for a condition which has posed a diagnostic challenge for decades.

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Effectiveness and cost-effectiveness of a health systems intervention for latent tuberculosis infection management (ACT4): a cluster-randomised trial

Olivia Oxlade[1], Andrea Benedetti[1], Mênonli Adjobimey[2], Hannah Alsdurf[1], Severin Anagonou[3], Victoria J Cook[4], Dina Fisher[5], Greg J Fox[6], Federica Fregonese[1], Panji Hadisoemarto[7], Philip C Hill[8], James Johnston[4], Faiz Ahmad Khan[1], Richard Long[9], Nhung V Nguyen[10], Thu Anh Nguyen[11], Joseph Obeng[12], Rovina Ruslami[7], Kevin Schwartzman[1], Anete Trajman[13], Chantal Valiquette[1], Dick Menzies[14]

Abstract

Background: Reaching the UN General Assembly High-Level Meeting on Tuberculosis target of providing tuberculosis preventive treatment to at least 30 million people by 2022, including 4 million children under the age of 5 years and 20 million other household contacts, will require major efforts to strengthen health systems. The aim of this study was to evaluate the effectiveness and cost-effectiveness of a health systems intervention to strengthen management for latent tuberculosis infection (LTBI) in household contacts of confirmed tuberculosis cases.

Methods: ACT4 was a cluster-randomised, open-label trial involving 24 health facilities in Benin, Canada, Ghana, Indonesia, and Vietnam randomly assigned to either a three-phase intervention (LTBI programme evaluation, local decision making, and strengthening activities) or control (standard LTBI care). Tuberculin and isoniazid were provided to control and intervention sites if not routinely available. Randomisation was stratified by country and restricted to ensure balance of index patients with tuberculosis by arm and country. The primary outcome was the number of household contacts who initiated tuberculosis preventive treatment at each health facility within 4 months of the diagnosis of the index case, recorded in the first or last 6 months of our 20-month study. To ease interpretation, this number was standardised per 100 newly diagnosed index patients with tuberculosis. Analysis was by intention to treat. Masking of staff at the coordinating centre and sites was not possible; however, those analysing data were masked to assignment of intervention or control. An economic analysis of the intervention was done in parallel with the trial. ACT4 is registered at ClinicalTrials.gov, NCT02810678.

Findings: The study was done between Aug 1, 2016, and March 31, 2019. During the first 6 months of the study the crude overall proportion of household contacts initiating tuberculosis preventive treatment out of those eligible at intervention sites was 0·21. After the implementation of programme strengthening activities, the proportion initiating tuberculosis preventive treatment increased to 0·35. Overall, the number of household contacts initiating tuberculosis preventive treatment per 100 index patients with tuberculosis increased between study phases in intervention sites (adjusted rate difference 60, 95% CI 4 to 116), while control sites showed no statistically significant change (-12, -33 to 10). There was a difference in rate differences of 72 (95% CI 10 to 134) contacts per 100 index patients with tuberculosis initiating preventive treatment associated with the intervention.

The total cost for the intervention, plus LTBI clinical care per additional contact initiating treatment was estimated to be CA$1348 (range 724 to 9708).
Interpretation: A strategy of standardised evaluation, local decision making, and implementation of health systems strengthening activities can provide a mechanism for scale-up of tuberculosis prevention, particularly in low-income and middle-income countries.

Clin Infect Dis. 2021 Jun 1;72(11):e784-e790.
doi: 10.1093/cid/ciaa1482.

Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living With Human Immunodeficiency Virus

Gerhard Theron[1], Grace Montepiedra[2], Lisa Aaron[2], Katie McCarthy[3], Nahida Chakhtoura[4], Patrick Jean-Philippe[5], Bonnie Zimmer[6], Amy James Loftis[7], Tsungai Chipato[8], Teacler Nematadzira[9], Mandisa Nyati[10], Carolyne Onyango-Makumbi[11], Gaerolwe Masheto[12], James Ngocho[13], Fuanglada Tongprasert[14 15], Sandesh Patil[16], Dominique Lespinasse[17], Adriana Weinberg[18], Amita Gupta[19]

Abstract
Background: International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1078, a randomized noninferiority study designed to compare the safety of starting isoniazid preventive therapy (IPT) in women living with human immunodeficiency virus (HIV) either during pregnancy or after delivery, showed that IPT during pregnancy increased the risk of composite adverse pregnancy outcomes, but not individual outcomes. Many known factors are associated with adverse pregnancy outcomes: these factors' associations and effect modifications with IPT and pregnancy outcomes were examined.
Methods: Pregnant women living with HIV from 8 countries with tuberculosis incidences >60/100 000 were randomly assigned to initiate 28 weeks of IPT either during pregnancy or at 12 weeks after delivery. Using univariable and multivariable logistic regression and adjusting for factors associated with pregnancy outcomes, composite and individual adverse pregnancy outcome measures were analyzed.
Results: This secondary analysis included 925 mother-infant pairs. All mothers were receiving antiretrovirals. The adjusted odds of fetal demise, preterm delivery (PTD), low birth weight (LBW), or a congenital anomaly (composite outcome 1) were 1.63 times higher among women on immediate compared to deferred IPT (95% confidence interval [CI], 1.15-2.31). The odds of fetal demise, PTD, LBW, or neonatal death within 28 days (composite outcome 2) were 1.62 times higher among women on immediate IPT (95% CI, 1.14-2.30). The odds of early neonatal death within 7 days, fetal demise, PTD, or LBW (composite outcome 3) were 1.74 times higher among women on immediate IPT (95% CI, 1.22-2.49).
Conclusions: We confirmed higher risks of adverse pregnancy outcomes associated with the initiation of IPT during pregnancy, after adjusting for known risk factors for adverse pregnancy outcomes.

N Engl J Med. 2020 Jul 23;383(4):359-368.
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Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease

Davaasambuu Ganmaa[1], Buyanjargal Uyanga[1], Xin Zhou[1], Garmaa Gantsetseg[1], Baigali Delgerekh[1], Davaasambuu Enkhmaa[1], Dorjnamjil Khulan[1], Saranjav Ariunzaya[1], Erdenebaatar Sumiya[1], Batbileg Bolortuya[1], Jutmaan Yanjmaa[1], Tserenkhuu Enkhtsetseg[1], Ankhbat Munkhzaya[1], Murneren Tunsag[1], Polyna Khudyakov[1], James A Seddon[1], Ben J Marais[1], Ochirbat Batbayar[1], Ganbaatar Erdenetuya[1], Bazarsaikhan Amarsaikhan[1], Donna Spiegelman[1], Jadambaa Tsolmon[1], Adrian R Martineau[1]

Abstract

Background: Vitamin D metabolites support innate immune responses to *Mycobacterium tuberculosis*. Data from phase 3, randomized, controlled trials of vitamin D supplementation to prevent tuberculosis infection are lacking.

Methods: We randomly assigned children who had negative results for *M. tuberculosis* infection according to the QuantiFERON-TB Gold In-Tube assay (QFT) to receive a weekly oral dose of either 14,000 IU of vitamin D_3 or placebo for 3 years. The primary outcome was a positive QFT result at the 3-year follow-up, expressed as a proportion of children. Secondary outcomes included the serum 25-hydroxyvitamin D (25[OH]D) level at the end of the trial and the incidence of tuberculosis disease, acute respiratory infection, and adverse events.

Results: A total of 8851 children underwent randomization: 4418 were assigned to the vitamin D group, and 4433 to the placebo group; 95.6% of children had a baseline serum 25(OH)D level of less than 20 ng per milliliter. Among children with a valid QFT result at the end of the trial, the percentage with a positive result was 3.6% (147 of 4074 children) in the vitamin D group and 3.3% (134 of 4043) in the placebo group (adjusted risk ratio, 1.10; 95% confidence interval [CI], 0.87 to 1.38; P = 0.42). The mean 25(OH)D level at the end of the trial was 31.0 ng per milliliter in the vitamin D group and 10.7 ng per milliliter in the placebo group (mean between-group difference, 20.3 ng per milliliter; 95% CI, 19.9 to 20.6). Tuberculosis disease was diagnosed in 21 children in the vitamin D group and in 25 children in the placebo group (adjusted risk ratio, 0.87; 95% CI, 0.49 to 1.55). A total of 29 children in the vitamin D group and 34 in the placebo group were hospitalized for treatment of acute respiratory infection (adjusted risk ratio, 0.86; 95% CI, 0.52 to 1.40). The incidence of adverse events did not differ significantly between the two groups.

Conclusions: Vitamin D supplementation did not result in a lower risk of tuberculosis infection, tuberculosis disease, or acute respiratory infection than placebo among vitamin D-deficient schoolchildren in Mongolia

Typhus

Urinary tract infection

Urology

Vaccines and immunization

Vaccine coverage and administration

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Effect of vaccine reminder and tracker bracelets on routine childhood immunization coverage and timeliness in urban Pakistan (2017-18): a randomized controlled trial

Danya Arif Siddiqi[1], Rozina Feroz Ali[2], Mehr Munir[2], Mubarak Taighoon Shah[2], Aamir Javed Khan[3 4], Subhash Chandir[3 2 4]

Abstract

Background: Inability to track children's vaccination history coupled with parents' lack of awareness of vaccination due dates compounds the problem of low immunization coverage and timeliness in developing countries. We evaluated the impact of two types of silicone immunization reminder bracelets for children in improving immunization coverage and timeliness of Pentavalent-3 and the Measles-1 vaccines.

Methods: Children < 3 months were enrolled in either of the 2 intervention groups (Alma Sana Bracelet Group and Star Bracelet Group) or the Control group. Children in the intervention groups were provided the two different bracelets at the time of recruitment. Each time the child visited the immunization center, a hole was perforated in the silicone bracelet to denote vaccine administration. Each child was followed up till administration of Measles-1 vaccine or till 12 months of age (if they did not come to the center for vaccination). Data was analyzed using the intention-to-treat population between groups. The unadjusted and adjusted Risk Ratios (RR) and 95% confidence interval (CI) for Pentavalent-3 and Measles-1 coverage at 12 months of age were estimated through bivariate and multivariate analysis. Time-to-Pentavalent-3 and Measles-1 immunization curves were calculated using the Kaplan-Meier method.

Results: A total of 1,445 children were enrolled in the study between July 19, 2017 and October 10, 2017. Baseline characteristics among the three groups were similar. Up-to-date coverage for the Pentavalent-3 /Measles-1 vaccine at 12 months of age was 84.6%/72.0%, 85.4%/70.5% and 83.0%/68.5% in Alma Sana Bracelet group, Star Bracelet group and Control group respectively but the differences were not statistically significant. In the multivariate analysis, neither the Alma Sana bracelet (adjusted RR = 1.01; 95% CI: 0.96-1.06), (adjusted RR: 1.05; 95% CI: 0.97-1.13) nor the Star bracelet (adjusted RR = 1.01; 95% CI: 0.96-1.06) (adjusted RR: 1.03; 95% CI: 0.95-1.11) was significantly associated with Pentavalent-3 vaccination or Measles-1 vaccination.

Conclusion: Although we did not observe any significant impact of the bracelets on improved immunization coverage and timeliness, our findings add to the existing literature on innovative, low cost reminders for health and make several suggestions for enhancing practical implementation of these tools.

J Glob Health. 2021 Jan 31;11:04004.
doi: 10.7189/jogh.11.04004.

How the use of vaccines outside the cold chain or in controlled temperature chain contributes to improving immunization coverage in low- and middle-income countries (LMICs): A scoping review of the literature

Ibrahim K Dadari[1,2], Janice C Zgibor[1]

Abstract

Background: Most vaccines are recommended for storage at temperatures of +2°C to +8°C to maintain potency. Immunization supply chain bottlenecks constraints reaching populations with life-saving vaccines. The World Health Organization permits the use of vaccines outside the cold chain as "controlled temperature chain (CTC)" upon meeting certain conditions and has set targets to license more vaccines CTC by 2020.

Objectives: This scoping review aims to explore and synthesize the evidence in the literature on how the use of vaccines outside the cold chain or in a controlled temperature chain increases immunization coverage in low and middle-income countries (LMICs), with a focus on the timelines of the Global Vaccine Action Plan (2011-2020).

Methods: A systematic search of three online databases (PubMed, Embase, and Web of Science) due to their broad coverage of global health sciences retrieved 173 original peer-reviewed articles, of which 13 were included in the review having met our inclusion criteria.

Results: The majority of the studies were conducted in Africa (n = 9), followed by Asia (n = 3), and the least in the Pacific (n = 1). The different study designs captured included four non-randomized trials, three randomized trials, two simulation models, two cross-sectional studies, and one cohort study. Reported benefits included increased coverage, logistical ease, cost savings while vaccines remain potent.

Conclusion: Currently, only two vaccines have been licensed to be stored CTC. More needs to be done to get additional vaccines licensed for CTC and disseminate operational guidance to operationalize its use in low- and middle-income countries.

Hum Vaccin Immunother. 2021 Jun 3;17(6):1703-1713.
doi: 10.1080/21645515.2020.1836917. Epub 2020 Dec 16.

Backfire effect of salient information on vaccine take-up experimental evidence from scared-straight intervention in rural northern Nigeria

Ryoko Sato[1], Yoshito Takasaki[2]

Abstract

Vaccination is the most cost-effective way to prevent mothers and infants from contracting tetanus. However, developing countries struggle with the persistent low take-up of vaccination. The low risk perceptions of disease can be one of the barriers to vaccination. One way to increase the risk perceptions of disease is to use salient loss-framed messages to highlight negative consequences of not getting vaccinated. We conducted a randomized controlled trial among 1,660 women in 80 villages in northeastern Nigeria. Respondents were randomly assigned to view one of two flipcharts: (1) control flipcharts, which contained written explanation about the severity of the disease, or (2) `scared-straight' flipcharts that contain the salient information about the disease severity in addition to the written explanation about the severity of the disease. Additionally, respondents were provided randomly assigned amounts of cash incentives. The scared-straight intervention backfired

among women with no previous experience of tetanus vaccination: it decreased their vaccine take-up by 3.7-6.1 percentage points, even though it increased their perceived risk of disease and their fear level. The negative effect of the scared-straight intervention is the most prevalent among women who received the lowest amount of cash incentive. Women without experience of tetanus vaccination might have responded to the scared-straight flipcharts by denying the information provided because the flipcharts were too frightening. The use of the scared-straight tactic is not recommended to aim for the improved take-up of vaccination in developing countries where people might face budget constraints for achieving desirable behaviors.

Implement Sci Commun. 2020 Oct 8;1:88.
doi: 10.1186/s43058-020-00077-7. eCollection 2020.

Implementation fidelity and acceptability of an intervention to improve vaccination uptake and child health in rural India: a mixed methods evaluation of a pilot cluster randomized controlled trial

Myriam Cielo Pérez[1,2], Dinesh Chandra[3], Georges Koné[4], Rohit Singh[5], Valery Ridde[6,7], Marie-Pierre Sylvestre[1,2], Aaditeshwar Seth[5,8], Mira Johri[1,9]

Abstract

Background: The Tika Vaani intervention, an initiative to improve basic health knowledge and empower beneficiaries to improve vaccination uptake and child health for underserved rural populations in India, was assessed in a pilot cluster randomized trial. The intervention was delivered through two strategies: mHealth (using mobile phones to send vaccination reminders and audio-based messages) and community mobilization (face-to-face meetings) in rural Indian villages from January to September 2018. We assessed acceptability and implementation fidelity to determine whether the intervention delivered in the pilot trial can be implemented at a larger scale.

Methods: We adapted the Conceptual Framework for implementation fidelity to assess acceptability and fidelity of the pilot interventions using a mixed methods design. Quantitative data sources include a structured checklist, household surveys, and mobile phone call patterns. Qualitative data came from field observations, intervention records, semi-structured interviews and focus groups with project recipients and implementers. Quantitative analyses assessed whether activities were implemented as planned, using descriptive statistics to describe participant characteristics and the percentage distribution of activities. Qualitative data were analyzed using content analysis and in the light of the implementation fidelity model to explore moderating factors and to determine how well the intervention was received.

Results: Findings demonstrated high (86.7%) implementation fidelity. A total of 94% of the target population benefited from the intervention by participating in a face-to-face group meeting or via mobile phone. The participants felt that the strategies were useful means for obtaining information. The clarity of the intervention theory, the motivation, and commitment of the implementers as well as the periodic meetings of the supervisors largely explain the high level of fidelity obtained. Geographic distance, access to a mobile phone, level of education, and gender norms are contextual factors that contributed to heterogeneity in participation.

Conclusions: Although the intervention was evaluated in the context of a randomized trial that could explain the high level of fidelity obtained, this evaluation provides confirmatory evidence that the results of the study reflect the underlying theory. The mobile platform coupled with community mobilization was well-received by the participants and could be a useful way to improve health knowledge and change behavior.

Environ Health Perspect. 2020 Aug;128(8):87002.
doi: 10.1289/EHP6517. Epub 2020 Aug 10.

Serum Perfluoroalkyl Substances, Vaccine Responses, and Morbidity in a Cohort of Guinea-Bissau Children

Clara Amalie Gade Timmermann[1], Kristoffer Jarlov Jensen[2 3], Flemming Nielsen[1], Esben Budtz-Jørgensen[4], Fiona van der Klis[5], Christine Stabell Benn[2 6], Philippe Grandjean[1 7], Ane Bærent Fisker[2 6 8]

Abstract

Background: Perfluoroalkyl substances (PFAS) are a group of widely used persistent chemicals with suspected immunotoxic effects.

Objectives: The present study aimed to examine the association between infant PFAS exposure and antibody responses to measles vaccination as well as morbidity in a low-income country.

Methods: In a randomized controlled trial, children from Guinea-Bissau, West Africa, were followed from inclusion (4-7 months of age) through 2 years of age. Half the children received two measles vaccinations (at inclusion and at 9 months of age), and the other half received only one (at 9 months of age). In a subset of 237 children, six PFAS were quantified in serum at inclusion, and measles antibody concentrations were assessed at inclusion and at approximately 9 months and 2 years of age. At inclusion and at the 9-month visit, mothers were interviewed about infant morbidity.

Results: All but one child had detectable serum concentrations of all six PFAS, although levels were lower than seen elsewhere. A doubling in perfluorooctane sulfonic acid (PFOS) and perfluorodecanoic acid (PFDA) were associated with 21% (95% CI: 2, 37%) and 25% (95% CI: 1, 43%), respectively, lower measles antibody concentrations at the 9-month visit among the children who had received a measles vaccine at inclusion. Elevated serum PFAS concentrations were also associated with reduced prevaccination measles antibody concentrations and increased morbidity.

Discussion: The present study documents that PFAS exposure has reached West Africa and that infants show PFAS-associated increases in morbidity and decreases in measles-specific antibody concentrations before and after vaccination.

Vaccine-related adverse effects

BCG vaccine

(See also Vaccine - Tuberculosis vaccine)

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BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial

Sarah Prentice[1], Beatrice Nassanga[2], Emily L Webb[3], Florence Akello[2], Fred Kiwudhu[2], Hellen Akurut[2], Alison M Elliott[4], Rob J W Arts[5], Mihai G Netea[6], Hazel M Dockrell[7], Stephen Cose[8], Delayed BCG Study Team

Abstract

Background: Trials done in infants with low birthweight in west Africa suggest that BCG vaccination reduces all-cause mortality in the neonatal period, probably because of heterologous protection against non-tuberculous infections. This study investigated whether BCG alters all-cause infectious disease morbidity in healthy infants in a different high-mortality setting, and explored whether the changes are mediated via trained innate immunity.

Methods: This was an investigator-blind, randomised, controlled trial done at one hospital in Entebbe, Uganda. Infants who were born unwell (ie, those who were not well enough to be discharged directly home from the labour ward because they required medical intervention), with major congenital malformations, to mothers with HIV, into families with known or suspected tuberculosis, or for whom cord blood samples could not be taken, were excluded from the study. Any other infant well enough to be discharged directly from the labour ward was eligible for inclusion, with no limitation on gestational age or birthweight. Participants were recruited at birth and randomly assigned (1:1) to receive standard dose BCG 1331 (BCG-Danish) on the day of birth or at age 6 weeks (computer-generated randomisation, block sizes of 24, stratified by sex). Investigators and clinicians were masked to group assignment; parents were not masked. Participants were clinically followed up to age 10 weeks and contributed blood samples to one of three immunological substudies. The primary clinical outcome was physician-diagnosed non-tuberculous infectious disease incidence. Primary immunological outcomes were histone trimethylation at the promoter region of TNF, IL6, and IL1B; ex-vivo production of TNF, IL-6, IL-1β, IL-10, and IFNγ after heterologous stimulation; and transferrin saturation and hepcidin levels. All outcomes were analysed in the modified intention-to-treat population of all randomly assigned participants except those whose for whom consent was withdrawn. This trial is registered with the International Standard Randomised Controlled Trial Number registry (#59683017).

Findings: Between Sept 25, 2014, and July 31, 2015, 560 participants were enrolled and randomly assigned to receive BCG at birth (n=280) or age 6 weeks (n=280). 12 participants assigned to receive BCG at birth and 11 participants assigned to receive BCG at age 6 weeks were withdrawn from the study by their parents shortly after randomisation and were not included in analyses. During the first 6 weeks of life before the infants in the delayed vaccination group received BCG vaccination, physician-diagnosed non-tuberculous infectious disease incidence was lower in infants in the BCG at birth group than in the delayed group (98 presentations in the BCG at birth group vs 129 in the delayed BCG group; hazard ratio [HR] 0·71 [95% CI 0·53-0·95], p=0·023). After BCG in the delayed group (ie, during the age 6-10 weeks follow-up), there was no significant difference in non-tuberculous infectious disease incidence between the groups (88 presentations vs 76 presentations; HR 1·10 [0·87-1·40], p=0·62). BCG at birth inhibited the increase in histone trimethylation at the TNF promoter in peripheral blood mononuclear cells occurring in the first 6 weeks of life.

H3K4me3 geometric mean fold-increases were 3·1 times lower at the TNF promoter (p=0·018), 2·5 times lower at the IL6 promoter (p=0·20), and 3·1 times lower at the IL1B promoter (p=0·082) and H3K9me3 geometric mean fold-increases were 8·9 times lower at the TNF promoter (p=0·0046), 1·2 times lower at the IL6 promoter (p=0·75), and 4·6 times lower at the IL1B promoter (p=0·068), in BCG-vaccinated (BCG at birth group) versus BCG-naive (delayed BCG group) infants. No clear effect of BCG on ex-vivo production of TNF, IL-6, IL-1β, IL-10, and IFNγ after heterologous stimulation, or transferrin saturation and hepcidin concentration, was detected (geometric mean ratios between 0·68 and 1·68; p≥0·038 for all comparisons).
Interpretation: BCG vaccination protects against non-tuberculous infectious disease during the neonatal period, in addition to having tuberculosis-specific effects. Prioritisation of BCG on the first day of life in high-mortality settings might have significant public-health benefits through reductions in all-cause infectious morbidity and mortality.

Clin Infect Dis. 2020 Nov 5;71(8):1883-1893.
doi: 10.1093/cid/ciz1080.
Early Vaccination With Bacille Calmette-Guérin-Denmark or BCG-Japan Versus BCG-Russia to Healthy Newborns in Guinea-Bissau: A Randomized Controlled Trial
Frederik Schaltz-Buchholzer[1 2 3], Morten Bjerregaard-Andersen[2 3], Christian Bjerregård Øland[3], Christian Golding[2 3], Elise Brenno Stjernholm[2 3], Ivan Monteiro[2], Peter Aaby[2], Christine Stabell Benn[1 2 3 4]
Abstract
Background: Bacille Calmette-Guérin (BCG) vaccination remains a cornerstone against tuberculosis. Randomized controlled trials (RCTs) have demonstrated that BCG-Denmark lowers all-cause mortality, but a recent RCT found no effect of BCG-Russia. Observational studies indicate that the genetically divergent BCG strains have different effects.
Methods: This was a parallel-group, open-label RCT conducted at the National Hospital in Guinea-Bissau. Healthy neonates were randomized 1:1 to BCG-Denmark (2851 randomized, 2840 analyzed) vs BCG-Russia (2845 randomized, 2837 analyzed). We hypothesized that BCG-Denmark would reduce morbidity (primary outcome) and mortality while inducing more BCG reactions and purified protein derivative (PPD) responses (secondary outcomes). Halfway through the trial, production of BCG-Denmark was halted, and the trial continued comparing BCG-Japan (3191 neonates randomized, 3184 analyzed) with BCG-Russia (3170 randomized, 3160 analyzed). Mortality and morbidity data were collected by telephone, at home visits, and at the National Hospital and assessed in Cox models providing 6-week mortality rate ratios (MRRs) and hospitalization incidence rate ratios (IRRs).
Results: By age 6 weeks, there were 140 and 130 admissions among neonates vaccinated with BCG-Denmark and BCG-Russia, respectively (IRR, 1.08 [95% confidence interval {CI}, .84-1.37]). For BCG-Japan, there were 185 admissions vs 161 admissions for BCG-Russia (IRR, 1.15 [95% CI, .93-1.43]). The 6-week mortality did not differ: BCG-Denmark/BCG-Russia (MRR, 1.15 [95% CI, .74-1.80]); BCG-Japan/BCG-Russia (MRR, 0.71 [95% CI, .43-1.19]). BCG-Denmark and BCG-Japan induced more BCG scars and PPD reactions than BCG-Russia.
Conclusions: BCG strains did not affect morbidity. BCG-Denmark and BCG-Japan were more immunogenic than BCG-Russia by the measures traditionally viewed as surrogates for successful immunization. The implications of strain differences for tuberculosis protection and overall health warrant further study.

Cholera vaccine

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Effectiveness of a killed whole-cell oral cholera vaccine in Bangladesh: further follow-up of a cluster-randomised trial

Mohammad Ali[1], Firdausi Qadri[2], Deok Ryun Kim[3], Md Taufiqul Islam[4], Justin Im[3], Faisal Ahmmed[4], Ashraful Islam Khan[4], K Zaman[4], Florian Marks[5], Jerome H Kim[3], John D Clemens[6]

Abstract

Background: Killed whole-cell oral cholera vaccines (OCVs) are widely used for prevention of cholera in developing countries. However, few studies have evaluated the protection conferred by internationally recommended OCVs for durations beyond 2 years of follow-up.

Methods: In this study, we followed up the participants of a cluster-randomised controlled trial for 2 years after the end of the original trial. Originally, we had randomised 90 geographical clusters in Dhaka slums in Bangladesh in equal numbers (1:1:1) to a two-dose regimen of OCV alone (targeted to people aged 1 year or older), a two-dose regimen of OCV plus a water-sanitation-hygiene (WASH) intervention, or no intervention. There was no masking of group assignment. The WASH intervention conferred little additional protection to OCV and was discontinued at 2 years of follow-up. Surveillance for severe cholera was continued for 4 years. Because of the short duration and effect of the WASH intervention, we combined the two OCV intervention groups. The primary outcomes were OCV overall protection (protection of all members of the intervention clusters) and total protection (protection of individuals who got vaccinated in the intervention clusters) against severe cholera, which we assessed by multivariable survival models appropriate for cluster-randomised trials. This trial is registered on ClinicalTrials.gov, NCT01339845.

Findings: The study was done between April 17, 2011, and Nov 1, 2015. 268 896 participants were present at the time of the first dose, with 188 206 in the intervention group and 80 690 in the control group. OCV coverage of the two groups receiving OCV was 66% (123 659 of 187 214 participants). During 4 years of follow-up, 441 first episodes of severe cholera were detected (243 episodes in the vaccinated groups and as 198 episodes in the unvaccinated group). Overall OCV protection was 36% (95% CI 19 to 49%) and total OCV protection was 46% (95% CI 32 to 58). Cumulative total vaccine protection was notably lower for people vaccinated before the age of 5 years (24%; -30 to 56) than for people vaccinated at age 5 years or older (49%; 35 to 60), although the differences in protection for the two age groups were not significant (p=0·3308). Total vaccine protection dropped notably (p=0·0115) after 3 years in children vaccinated at 1-4 years of age.

Interpretation: These findings provide further evidence of long-term effectiveness of killed whole-cell OCV, and therefore further support for the use of killed whole-cell OCVs to control endemic cholera, but indicate that protection is shorter-lived in children vaccinated before the age of 5 years than in people vaccinated at the age of 5 years or older.

Dengue vaccine

Lancet Infect Dis. 2021 Apr;21(4):517-528.
doi: 10.1016/S1473-3099(20)30767-2. Epub 2020 Nov 16.

Immunogenicity and safety of simplified vaccination schedules for the CYD-TDV dengue vaccine in healthy individuals aged 9-50 years (CYD65): a randomised, controlled, phase 2, non-inferiority study

Diana Leticia Coronel-MartÍnez[1], Juliana Park[2], Eduardo López-Medina[3], María Rosario Capeding[4], Andrés Angelo Cadena Bonfanti[5], María Cecilia Montalbán[6], Isabel Ramírez[7], María Liza Antoinette Gonzales[8], Carlos A DiazGranados[9], Betzana Zambrano[10], Gustavo Dayan[11], Stephen Savarino[11], Zhenghong Chen[12], Hao Wang[12], Sunny Sun[12], Matthew Bonaparte[11], Andrey Rojas[13], Jenny Carolina Ramírez[13], Mae Ann Verdan[14], Fernando Noriega[11]

Abstract

Background: Three doses of the licensed tetravalent dengue vaccine CYD-TDV (Dengvaxia, Sanofi Pasteur, Lyon France) are immunogenic and effective against symptomatic dengue in individuals aged 9 years and older who are dengue seropositive. Previous trials have provided some evidence that antibody responses elicited after just one dose or two doses of CYD-TDV might be similar to those elicited after three doses. We compared antibody responses following one-dose, two-dose, and three-dose vaccination regimens in individuals who were dengue seropositive at baseline up to 1 year after the last injection.

Methods: In this randomised, controlled, phase 2, non-inferiority study (CYD65), healthy individuals aged 9-50 years were recruited from the community in three sites in Colombia and three sites in the Philippines. Participants were randomly assigned (1:1:1), using a permuted block method with stratification by site and age group, to receive, at 6-month intervals (on day 0, month 6, and month 12), three doses of CYD-TDV (three-dose group), one dose of placebo (on day 0) and two doses of CYD-TDV (at months 6 and 12; two-dose group), or two doses of placebo (on day 0 and month 6) and one dose of CYD-TDV (at month 12; one-dose group). Each dose of CYD-TDV was 0·5 mL, administered subcutaneously into the deltoid of the upper arm. Participants, study staff, investigators, and the funder were masked to group assignment. The co-primary endpoints were geometric mean titres (GMTs) of neutralising antibodies against each dengue virus serotype at 28 days and 1 year after the last vaccine injection. After a protocol amendment during the conduct of the study, the original co-primary objectives of non-inferiority of the one-dose and two-dose groups to the three-dose group were altered to include non-inferiority of the two-dose group to the three-dose group only, to be assessed in individuals who were dengue seropositive at baseline. Non-inferiority was shown if the lower limit of the 95% CI for the ratio of GMTs (GMR) at 28 days and 1 year between groups was more than 0·5 for each serotype. The analysis of the coprimary objectives was done in the per-protocol analysis dataset, which included all participants who had been vaccinated, had no protocol deviations, and had a valid serology test result for at least one dengue serotype at 28 days after the third injection. Safety was assessed throughout in all participants who received at least one injection of study drug, regardless of serostatus. This trial is registered with ClinicalTrials.gov, NCT02628444, and is closed to accrual.

Findings: Between May 2, 2016, and Sept 16, 2016, we recruited and enrolled 1050 individuals, of whom 1048 received at least one injection and 993 had at least one blood

sample taken (full-analysis dataset; 333 in three-dose group, 328 in two-dose group, and 332 in one-dose group). 860 (86·6%) of 993 participants in the full-analysis dataset were dengue seropositive at baseline. Non-inferiority (two dose vs three dose) was shown for each serotype at both 28 days and 1 year among dengue-seropositive participants (number of participants assessed: 272 [two-dose group], 265 [three-dose group] at 28 days; and 190 [two-dose group], 185 [three-dose group] at 1 year). At 28 days after the last injection, neutralising antibody GMTs were 899 (95% CI 752-1075) in the two-dose group versus 822 (700-964) in the three dose group against dengue serotype 1 (GMR 1·09 [95% CI 0·86-1·39]); 869 (754-1002) versus 875 (770-995) against serotype 2 (GMR 0·99 [0·82-1·20]); 599 (524-685) versus 610 (535-694) against serotype 3 (GMR 0·98 [0·82-1·18]); and 510 (453-575) versus 531 (470-601) against serotype 4 (GMR 0·96 [0·81-1·14]). At year 1, GMTs had decreased but remained above baseline for all serotypes: 504 (95% CI 403-630) in the two-dose group versus 490 (398-604) in the three-dose group against serotype 1 (GMR 1·03 [0·76-1·40]); 737 (611-888) versus 821 (704-957) against serotype 2 (GMR 0·90 [0·71-1·14]); 437 (368-519) versus 477 (405-561) against serotype 3 (GMR 0·92 [0·72-1·16]); and 238 (205-277) versus 270 (235-310) against serotype 4 (GMR 0·88 [0·72-1·09]). Reactogenicity profiles were similar across treatment groups. Most unsolicited adverse events after any injection were non-serious and systemic in nature. During the study, 60 serious adverse events were reported in 58 participants (14 in three-dose group, 26 in two-dose group, 18 in one-dose group), mostly infection and infestations or injury, poisoning, and procedural complications. No serious adverse events of special interest or admissions to hospital for dengue occurred. Two deaths occurred, unrelated to study treatment.

Interpretation: A two-dose CYD-TDV regimen might be an alternative to the licensed three-dose regimen in individuals who are dengue seropositive at baseline and aged 9 years and older. Vaccination with a reduced number of doses could lead to improved vaccine compliance and coverage, especially in low-resource settings.

Am J Trop Med Hyg. 2021 Jan;104(1):136-144.
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Zika and Dengue Interactions in the Context of a Large Dengue Vaccine Clinical Trial in Latin America

Betzana Zambrano[1], Fernando Noriega[2], Gustavo H Dayan[2], Doris Maribel Rivera[3], José Luis Arredondo[4], Humberto Reynales[5], Kleber Luz[6], Carmen Deseda[7], Matthew I Bonaparte[8], Edith Langevin[9], Yukun Wu[2], Margarita Cortés[10], Stephen Savarino[8], Carlos A DiazGranados[2]

Abstract

A phase III dengue vaccine trial including 9- to 16-year-olds in Latin America (NCT01374516) was ongoing at the time of a Zika outbreak. We explored interactions between dengue and Zika, in the context of dengue vaccination. Symptomatic virologically confirmed Zika (VCZ) was evaluated using acute-phase sera from febrile participants (January 2013-March 2018). Neutralizing antibody geometric mean titers (GMTs) were evaluated pre- and post-Zika outbreak (months 25 and 72) in 2,000 randomly selected participants. Baseline dengue serostatus was determined using the plaque reduction neutralization test or inferred post hoc using nonstructural protein 1 IgG ELISA at M13 (case-cohort analysis). Vaccine efficacy against VCZ and serologically suspected Zika (SSZ) was estimated. Overall, 239/10,157 (2.4%)

acute-phase samples were VCZ positive during the study. Dengue vaccine efficacy against VCZ was 27.8% (95% CI: 0.3; 47.7) among baseline dengue-seropositive participants. No vaccine effect was evident against SSZ. Zika antibody GMTs increased from pre- to post-Zika epidemic, with smaller increases observed for participants who were dengue seropositive at baseline than for those who were dengue seronegative: post-/pre-Zika GMT ratios for baseline dengue-seropositive participants were 21.5 (vaccine group) and 30.8 (placebo); and for dengue seronegatives, 88.1 and 89.5, respectively. Dengue antibody GMTs post-Zika were higher in dengue vaccine and placebo recipients with SSZ than those without SSZ in both dengue seropositives and seronegatives. Dengue vaccine did not enhance symptomatic Zika illness in dengue-seropositive individuals, rather it reduced the risk of VCZ. Zika infection boosted preexisting vaccine-induced or naturally occurring dengue-neutralizing antibodies.

Diptheria-tetanus-pertussus vaccine

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doi: 10.1016/j.vaccine.2020.08.058. Epub 2020 Sep 2.

Levels of antibodies specific to diphtheria toxoid, tetanus toxoid, and Haemophilus influenzae type b in healthy children born to Tdap-vaccinated mothers

Nasamon Wanlapakorn[1], Kirsten Maertens[2], Thanunrat Thongmee[3], Donchida Srimuan[3], Thaksaporn Thatsanathorn[3], Pierre Van Damme[2], Elke Leuridan[2], Yong Poovorawan[4]

Abstract

Introduction: Vaccination of pregnant women protects both women and their newborns against some infectious diseases. Thailand implemented tetanus toxoid (TT) vaccination of pregnant women in 1977, which was replaced by tetanus-diphtheria toxoid (dT) vaccination in 2005. The tetanus-diphtheria-acellular pertussis (Tdap) vaccine has been recommended for pregnant women at 27-36 weeks of gestation since 2012 in several countries. Data on antibody responses to diphtheria toxoid (DT), TT, and Hemophilus influenzae type b (Hib) induced by combined vaccines in children born to TT-vaccinated and/or Tdap-vaccinated mothers are limited.

Material and methods: We investigated anti-DT, anti-TT, and anti-Hib IgG responses in a cohort of Thai children (ClinicalTrial.gov NCT02408926) born to mothers who received a TT-containing and/or the Tdap vaccine during pregnancy. Children born to Tdap-vaccinated mothers were randomized to receive either a hexavalent (Infanrix-hexa) or pentavalent (Quinvaxem) vaccine, whereas children born to TT-vaccinated mothers received only Quinvaxem vaccine at 2, 4, 6, and 18 months of age. IgG levels were evaluated at birth (cord blood), 2 (pre-primary), 7 (post-primary), 18 (pre-booster), and 19 months of age (post-booster) using a commercially available enzyme-linked immunoassay.

Results: Seroprotective concentrations of anti-DT, anti-TT, and anti-Hib IgG were achieved in >90% and >99% of children following primary and booster vaccination, respectively. Among children born to Tdap-vaccinated mothers, the pentavalent vaccine induced higher levels of anti-Hib IgG than the hexavalent vaccine after primary and booster vaccination. Significantly higher anti-Hib IgG levels were observed among children receiving the pentavalent vaccine and who were born to TT-vaccinated mothers than among children receiving the pentavalent vaccine and born to Tdap-vaccinated mothers after primary and booster vaccination.

Conclusions: Vaccination with a TT-containing and/or the Tdap vaccine during pregnancy did not compromise the seroprotection rate achieved following primary and booster immunization in individuals receiving either the pentavalent or hexavalent vaccine.

Ebola vaccine

Trials. 2021 Jan 23;22(1):86.
doi: 10.1186/s13063-021-05035-9.

Partnership for Research on Ebola VACcination (PREVAC): protocol of a randomized, double-blind, placebo-controlled phase 2 clinical trial evaluating three vaccine strategies against Ebola in healthy volunteers in four West African countries

Moses Badio[#1], Edouard Lhomme[#2], Mark Kieh[1], Abdoul Habib Beavogui[3], Stephen B Kennedy[1], Seydou Doumbia[4], Bailah Leigh[5], Samba O Sow[6], Alpha Diallo[7], Daniela Fusco[7], Matthew Kirchoff[8], Monique Termote[2], Renaud Vatrinet[9], Deborah Wentworth[10], Helène Esperou[7], H Clifford Lane[8], Jerome Pierson[8], Deborah Watson-Jones[11], Céline Roy[1], Eric D'Ortenzio[9 12], Brian Greenwood[11], Genevieve Chêne[1], Laura Richert[1], James D Neaton[10], Yazdan Yazdanpanah[13 14], PREVAC study team

Abstract

Introduction: The Ebola virus disease (EVD) outbreak in 2014-2016 in West Africa was the largest on record and provided an opportunity for large clinical trials and accelerated efforts to develop an effective and safe preventative vaccine. Multiple questions regarding the safety, immunogenicity, and efficacy of EVD vaccines remain unanswered. To address these gaps in the evidence base, the Partnership for Research on Ebola Vaccines (PREVAC) trial was designed. This paper describes the design, methods, and baseline results of the PREVAC trial and discusses challenges that led to different protocol amendments.

Methods: This is a randomized, double-blind, placebo-controlled phase 2 clinical trial of three vaccine strategies against the Ebola virus in healthy volunteers 1 year of age and above. The three vaccine strategies being studied are the rVSVΔG-ZEBOV-GP vaccine, with and without a booster dose at 56 days, and the Ad26.ZEBOV,MVA-FN-Filo vaccine regimen with Ad26.ZEBOV given as the first dose and the MVA-FN-Filo vaccination given 56 days later. There have been 4 versions of the protocol with those enrolled in Version 4.0 comprising the primary analysis cohort. The primary endpoint is based on the antibody titer against the Ebola virus surface glycoprotein measured 12 months following the final injection.

Results: From April 2017 to December 2018, a total of 5002 volunteers were screened and 4789 enrolled. Participants were enrolled at 6 sites in four countries (Guinea, Liberia, Sierra Leone, and Mali). Of the 4789 participants, 2560 (53%) were adults and 2229 (47%) were children. Those < 18 years of age included 549 (12%) aged 1 to 4 years, 750 (16%) 5 to 11 years, and 930 (19%) aged 12-17 years. At baseline, the median (25th, 75th percentile) antibody titer to Ebola virus glycoprotein for 1090 participants was 72 (50, 116) EU/mL.

Discussion: The PREVAC trial is evaluating-placebo-controlled-two promising Ebola candidate vaccines in advanced stages of development. The results will address unanswered questions related to short- and long-term safety and immunogenicity for three vaccine strategies in adults and children.

Enterovirus 71 vaccine

Hepatitis A vaccine

Hepatitis B vaccine

Indian Pediatr. 2021 Mar 15;58(3):224-228.
Three vs Four Dose Schedule of Double Strength Recombinant Hepatitis-B Vaccine in HIV-infected Children: A Randomized Controlled Trial
Prachi Jain[1], Pooja Dewan[2], Sunil Gomber[1], Bineeta Kashyap[3], Alpana Raizada[4]
Objective: To compare seroprotection rates and the anti-HBs titers following primary immunization with double strength (20 µg) recombinant hepatitis B virus (rHBV) vaccine administered intramuscularly (IM) in a 3-dose (0, 1 and 6 months) vs 4-dose (0, 1, 2 and 6 months) schedule in HIV-infected children receiving antiretroviral therapy (ART). An accelerated 3-dose schedule (0, 1, 2 months) within the 4-dose group was also compared.
Design: Randomized controlled trial.
Setting: Pediatric ART clinic of a tertiary hospital in Delhi from November, 2017 to April, 2019.
Participants: Fifty (25 per group) HIV-infected children aged 18 months - 12 years receiving ART for at least 6 months who had not received any prior dose of HBV vaccine, and were anti-HBs negative.
Intervention: Group 1 received 20 µg of rHBV vaccine IM (in deltoid muscle) at 0, 1, and 6 months, and group 2 received 20 µg the same vaccine at 0, 1, 2 and 6 months.
Outcome variables: Anti-HBs titers and proportion of responders in 3-dose vs 4-dose group at seventh and twelfth month and at third month after an accelerated 3-dose schedule.
Results: Median (IQR) anti-HBs titers at the seventh month were significantly higher in group 2 [225.7 (151-300) IU/L] compared to group 1 [138.2 (35.2-250) IU/L], but were comparable at the 12th month. Seroprotection rates were comparable between group 2 and group 1 at 7th month (96% vs 80%; P=0.19) and 12th month (96% vs 88%; P=0.61). The proportion of good responders were also comparable between the groups at 7th month and 12th month (both P=0.29). Accelerated 3-dose schedule achieved comparable anti-HBs titers [179.9 (130.6-250) IU/L] and seroprotection rate (92%) one month after completion of schedule to the standard 3-dose + schedule.
Conclusions: A 3-dose double strength recombinant HBV vaccine schedule offers comparable seroprotection to 4-dose schedule for HIV-infected children receiving ART.

HIV vaccine

HPV vaccine

Vaccine. 2021 Apr 15;39(16):2224-2236.
doi: 10.1016/j.vaccine.2020.11.076. Epub 2021 Mar 18.
Systematic literature review of cross-protective effect of HPV vaccines based on data from randomized clinical trials and real-world evidence

Darron R Brown[1], Elmar A Joura[2], Glorian P Yen[3], Smita Kothari[4], Alain Luxembourg[5], Alfred Saah[6], Anuj Walia[7], Gonzalo Perez[8], Hanane Khoury[9], Danielle Badgley[9], Margaret Stanley[10]

Abstract

Background: The extent of cross-protection provided by currently licensed bivalent and quadrivalent HPV vaccines versus direct protection against HPV 31-, 33-, 45-, 52-, and 58-related disease is debated. A systematic literature review was conducted to establish the duration and magnitude of cross-protection in interventional and observational studies.

Methods: PubMed and Embase databases were searched to identify randomized controlled trials (RCT) and observational studies published between 2008 and 2019 reporting on efficacy and effectiveness of HPV vaccines in women against non-vaccine types 31, 33, 45, 52, 58, and 6 and 11 (non-bivalent types). Key outcomes of interest were vaccine efficacy against 6- and 12-month persistent infection or genital lesions, and type-specific genital HPV prevalence or incidence. RCT data were analyzed for the according-to-protocol (bivalent vaccine) or negative-for-14-HPV-types (quadrivalent vaccine) efficacy cohorts.

Results: Data from 23 RCTs and 33 observational studies evaluating cross-protection were extracted. RCTs assessed cross-protection in post-hoc analyses of small size subgroups. Among fully vaccinated, baseline HPV-naïve women, the bivalent vaccine showed statistically significant cross-protective efficacy, although with wide confidence intervals, against 6-month and 12-month persistent cervical infections and CIN2+ only consistently for HPV 31 and 45, with the highest effect observed for HPV 31 (range 64.6% [95% CI: 27.6 to 83.9] to 79.1% [97.7% CI: 27.6 to 95.9] for 6-month persistent infection; maximal follow-up 4.7 years). No cross-protection was shown in extended follow-up. The quadrivalent vaccine efficacy reached statistical significance for HPV 31 (46.2% [15.3-66.4]; follow-up: 3.6 years). Similarly, observational studies found consistently significant effectiveness only against HPV 31 and 45 with both vaccines.

Conclusions: RCTs and observational studies show that cross-protection is inconsistent across non-vaccine HPV types and is largely driven by HPV 31 and 45. Furthermore, existing data suggest that it wanes over time; its long-term durability has not been established.

Influenza vaccine

Clin Infect Dis. 2021 Jun 15;72(12):e959-e969.
doi: 10.1093/cid/ciaa1689.

Estimates of Inactivated Influenza Vaccine Effectiveness Among Children in Senegal: Results From 2 Consecutive Cluster-Randomized Controlled Trials in 2010 and 2011

Mbayame Nd Niang[1], Jonathan D Sugimoto[2,3,4], Aldiouma Diallo[5], Bou Diarra[5], Justin R Ortiz[6], Kristen D C Lewis[7], Kathryn E Lafond[8], M Elizabeth Halloran[2,9], Marc-Alain Widdowson[2,6,10], Kathleen M Neuzil[6], John C Victor[7]

Abstract

Background: We report results of years 2 and 3 of consecutive cluster-randomized controlled trials of trivalent inactivated influenza vaccine (IIV3) in Senegal.

Methods: We cluster-randomized (1:1) 20 villages to annual vaccination with IIV3 or inactivated poliovirus vaccine (IPV) of age-eligible residents (6 months-10 years). The primary outcome was total vaccine effectiveness against laboratory-confirmed influenza illness (LCI) among age-eligible children (modified intention-to-treat population [mITT]). Secondary

outcomes were indirect (herd protection) and population (overall community) vaccine effectiveness.
Results: We vaccinated 74% of 12 408 age-eligible children in year 2 (June 2010-April 11) and 74% of 11 988 age-eligible children in year 3 (April 2011-December 2011) with study vaccines. Annual cumulative incidence of LCI was 4.7 (year 2) and 4.2 (year 3) per 100 mITT child vaccinees of IPV villages. In year 2, IIV3 matched circulating influenza strains. The total effectiveness was 52.8% (95% confidence interval [CI], 32.3-67.0), and the population effectiveness was 36.0% (95% CI, 10.2-54.4) against LCI caused by any influenza strain. The indirect effectiveness against LCI by A/H3N2 was 56.4% (95% CI, 39.0-68.9). In year 3, 74% of influenza detections were vaccine-mismatched to circulating B/Yamagata and 24% were vaccine-matched to circulating A/H3N2. The year 3 total effectiveness against LCI was -14.5% (95% CI, -81.2-27.6). Vaccine effectiveness varied by type/subtype of influenza in both years.
Conclusions: IIV3 was variably effective against influenza illness in Senegalese children, with total and indirect vaccine effectiveness present during the year when all circulating strains matched the IIV3 formulation.

Vaccine. 2020 Aug 27;38(38):5979-5986.
doi: 10.1016/j.vaccine.2020.07.019. Epub 2020 Jul 31.

Efficacy and safety of a live attenuated influenza vaccine in Chinese healthy children aged 3-17 years in one study center of a randomized, double-blind, placebo-controlled phase 3 clinical trial, 2016/17 season

Shenyu Wang[1], Yihong Zheng[2], Xiongyuan Jin[3], Zhengkai Gan[4], Yanzhi Shao[5], Changlin Zhu[6], Xiaosong Hu[7], Zhenzhen Liang[8], Yingping Chen[9], Bo Xing[10], Huakun Lv[11], Na Xu[12]

Abstract
Background: No data on the safety and efficacy of a live attenuated influenza vaccine in China have ever been reported.
Methods: At a site of a phase 3 randomized, double-blind, placebo-controlled clinical trial in eastern China, eligible healthy children aged 3-17 years underwent randomization to receive live attenuated vaccine or placebo at a ratio of 1:1. The primary objective of the study was the prevention of laboratory-confirmed influenza illness during the surveillance period, starting on day 15 after vaccination.
Results: A total of 2000 participants were enrolled, with 998 receiving the vaccine and 1001 receiving placebo. Sixty-four cases of influenza-like illness were observed, of which, 44 were laboratory-confirmed (12 in vaccine group versus 32 in placebo group). Vaccine efficacy was 62.5% (95%CI: 27.6-80.6) against all types of influenza and 63.3% (95%CI: 27.5-81.5) against influenza H3N2 illness. 11 severe adverse events reported (7 in LAIV group versus 4 in placebo group) were all deemed to be non-vaccine-related. Adverse events occurred in 412 (41.3%) participants in the vaccine group versus 389 (38.9%; p = 0.274) participants in the placebo group. Significant increase incidence of fever was observed in participants in the vaccine group, especially in those aged 3-9 years.
Conclusions: The live attenuated influenza vaccine showed good efficacy and safety among 3- to 17-year-olds children during the 2016-2017 season at a site in eastern China

Vaccine. 2020 Nov 3;38(47):7526-7532.
doi: 10.1016/j.vaccine.2020.09.059. Epub 2020 Oct 2.

Immunogenicity of seasonal inactivated influenza and inactivated polio vaccines among children in Senegal: Results from a cluster-randomized trial

Mbayame Niang[1], Meagan E Deming[2], Deborah Goudiaby[1], Ousmane M Diop[3], Ndongo Dia[1], Aldiouma Diallo[4], Justin R Ortiz[5], Doudou Diop[6], Kristen D C Lewis[7], Kathryn E Lafond[8], Marc-Alain Widdowson[9], John C Victor[7], Kathleen M Neuzil[10]

Abstract

Data on influenza vaccine immunogenicity in children are limited from tropical developing countries. We recently reported significant, moderate effectiveness of a trivalent inactivated influenza vaccine (IIV) in a controlled, cluster-randomized trial in children in rural Senegal during 2009, a year of H3N2 vaccine mismatch (NCT00893906). We report immunogenicity of IIV3 and inactivated polio vaccine (IPV) from that trial. We evaluated hemagglutination inhibition (HAI) and polio antibody titers in response to vaccination of three age groups (6 through 35 months, 3 through 5 years, and 6 through 8 years). As all children were IIV naïve, each received two vaccine doses, although titers were assessed after only the first dose for subjects aged 6 through 8 years. Seroconversion rates (4-fold titer rise or increase from <1:10 to ≥1:40) were 74-87% for A/H1N1, 76-87% for A/H3N2, and 54-79% for B/Yamagata. Seroprotection rates (HAI titer ≥ 1:40) were 79-88% for A/H1N1, 88-96% for A/H3N2, and 52-74% for B/Yamagata. IIV responses were lowest in the youngest age group, and they were comparable between ages 3 through 5 years after two doses and 6 through 8 years after one dose. We found that baseline seropositivity (HAI titer ≥ 1:10) was an effect modifier of IIV response. Using a seroprotective titer (HAI titer ≥ 1:160) recommended for IIV evaluation in children, we found that among subjects who were seropositive at baseline, 69% achieved seroprotection for both A/H1N1 and A/H3N2, while among those who were seronegative at baseline, seroprotection was achieved in 11% for A/H1N1 and 22% for A/H3N2. The IPV group had high baseline polio antibody seropositivity and appropriate responses to vaccination. Our data emphasize the importance of a two-dose IIV3 series in vaccine naïve children. IIV and IPV vaccines were immunogenic in Senegalese children.

Vaccine. 2020 Oct 7;38(43):6826-6831.
doi: 10.1016/j.vaccine.2020.08.014. Epub 2020 Aug 17.

Assessment of indirect protection from maternal influenza immunization among non-vaccinated household family members in a randomized controlled trial in Sarlahi, Nepal

Kira L Newman[1], Laveta M Stewart[2], Emily M Scott[3], James M Tielsch[4], Janet A Englund[5], Subarna K Khatry[6], Luke C Mullany[2], Steven C LeClerq[7], Laxman Shrestha[8], Jane M Kuypers[9], Helen Y Chu[10], Joanne Katz[2]

Abstract

Influenza is a significant cause of morbidity and mortality worldwide, and the World Health Organization highly recommends maternal vaccination during pregnancy. The indirect effect of maternal vaccination on other close contacts other than newborns is unknown. To evaluate this, we conducted a nested substudy between 2011 and 2012 of influenza and acute respiratory illness (ARI) among household members of pregnant women enrolled in a randomized placebo-controlled trial of antenatal influenza vaccination in the rural district of

Sarlahi, Nepal. Women were assigned to receive influenza vaccination or placebo during pregnancy and then they and their household members were followed up to 6 months postpartum with weekly symptom surveillance and nasal swab collection. Swabs were tested by RT-PCR for influenza. Rates of laboratory-confirmed influenza and of ARI were compared between vaccine and placebo groups using generalized estimating equations with a Poisson link function. Overall, 1752 individuals in 520 households were eligible for inclusion. There were 82 laboratory-confirmed influenza illness episodes, for a rate of 7.0 per 100 person-years overall. Of the influenza strains able to be typed, 29 were influenza A, 40 were influenza B, and 6 were coinfections with influenza A and B. The rate did not differ significantly whether the household was in the vaccine or placebo group (rate ratio (RR) 1.37, 95% confidence interval (CI) 0.83-2.26). The rate of ARI was 28.5 per 100 person-years overall and did not differ by household group (RR 0.99, 95% CI 0.72-1.36). Influenza vaccination of pregnant women did not provide indirect protection of unvaccinated household members.

Japanese encephalitis virus vaccine

J Infect Dis. 2020 Oct 1;222(9):1478-1487.
doi: 10.1093/infdis/jiz672.

Persistence of Immune Responses With an Inactivated Japanese Encephalitis Single-Dose Vaccine, JENVAC and Interchangeability With a Live-Attenuated Vaccine

Krishna Mohan Vadrevu[1], Venugopal Potula[2], Vasant Khalatkar[3], Niranjana S Mahantshetty[4], Atish Shah[5], Raches Ella[1]

Abstract

Background: This study reports immunogenicity, safety, and interchangeability of a single-dose, inactivated, Vero-cell derived, JENVAC to the live-attenuated SA 14-14-2 vaccine in healthy children.

Methods: This phase 4, multicenter, open-label, randomized, control trial enrolled 360 children who were equally randomized to receive a single dose of either JENVAC or SA 14-14-2. Children were followed at various time points, until 2 years (day 720) postvaccination, upon which a subset from each group was divided and allocated to a receive a booster dose or the other vaccine.

Results: At all time points, immunological measures were statistically higher in the JENVAC group. In the interchangeability study, children receiving 2 doses of JENVAC reported significantly higher response compared with 2 doses of SA 14-14-2. No difference in adverse events was observed. These corroborate with excellent seroprotection after the first dose of an earlier JENVAC study.

Conclusions: A single-dose vaccination with JENVAC induces protective titers that persist up to 1 year. We report appreciable interchangeability between both vaccines, with JENVAC/JENVAC combination exhibiting the highest immune response. JENVAC is now licensed as a single-dose Japanese encephalitis vaccine.

Leishmaniasis vaccine

Mol Ther. 2021 Mar 27;S1525-0016(21)00149-0.
doi: 10.1016/j.ymthe.2021.03.020. Online ahead of print.

Safety and immunogenicity of ChAd63-KH vaccine in post-kala-azar dermal leishmaniasis patients in Sudan

Brima M Younis[1], Mohamed Osman[2], Eltahir A G Khalil[1], Francesco Santoro[3], Simone Furini[3], Rebecca Wiggins[2], Ada Keding[4], Monica Carraro[3], Anas E A Musa[1], Mujahid A A Abdarahaman[1], Laura Mandefield[4], Martin Bland[4], Toni Aebischer[5], Rhian Gabe[6], Alison M Layton[2], Charles J N Lacey[2], Paul M Kaye[7], Ahmed M Musa[8]

Abstract

Post-kala-azar dermal leishmaniasis (PKDL) is a chronic, stigmatizing skin condition occurring frequently after apparent clinical cure from visceral leishmaniasis. Given an urgent need for new treatments, we conducted a phase IIa safety and immunogenicity trial of ChAd63-KH vaccine in Sudanese patients with persistent PKDL. LEISH2a (ClinicalTrials.gov: NCT02894008) was an open-label three-phase clinical trial involving sixteen adult and eight adolescent patients with persistent PKDL (median duration, 30 months; range, 6-180 months). Patients received a single intramuscular vaccination of 1×10^{10} viral particles (v.p.; adults only) or 7.5×10^{10} v.p. (adults and adolescents), with primary (safety) and secondary (clinical response and immunogenicity) endpoints evaluated over 42-120 days follow-up. AmBisome was provided to patients with significant remaining disease at their last visit. ChAd63-KH vaccine showed minimal adverse reactions in PKDL patients and induced potent innate and cell-mediated immune responses measured by whole-blood transcriptomics and ELISpot. 7/23 patients (30.4%) monitored to study completion showed >90% clinical improvement, and 5/23 (21.7%) showed partial improvement. A logistic regression model applied to blood transcriptomic data identified immune modules predictive of patients with >90% clinical improvement. A randomized controlled trial to determine whether these clinical responses were vaccine-related and whether ChAd63-KH vaccine has clinical utility is underway.

Malaria vaccine

Lancet. 2021 May 5;S0140-6736(21)00943-0.
doi: 10.1016/S0140-6736(21)00943-0. Online ahead of print.

Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial

Mehreen S Datoo[1], Magloire H Natama[2], Athanase Somé[2], Ousmane Traoré[2], Toussaint Rouamba[2], Duncan Bellamy[3], Prisca Yameogo[2], Daniel Valia[2], Moubarak Tegneri[2], Florence Ouedraogo[2], Rachidatou Soma[2], Seydou Sawadogo[2], Faizatou Sorgho[2], Karim Derra[2], Eli Rouamba[2], Benedict Orindi[4], Fernando Ramos Lopez[1], Amy Flaxman[3], Federica Cappuccini[3], Reshma Kailath[3], Sean Elias[3], Ekta Mukhopadhyay[3], Andres Noe[3], Matthew Cairns[5], Alison Lawrie[1], Rachel Roberts[1], Innocent Valéa[2], Hermann Sorgho[2], Nicola Williams[6], Gregory Glenn[7], Louis Fries[7], Jenny Reimer[8], Katie J Ewer[3], Umesh Shaligram[9], Adrian V S Hill[10], Halidou Tinto[11]

Abstract

Background: Stalled progress in controlling Plasmodium falciparum malaria highlights the need for an effective and deployable vaccine. RTS,S/AS01, the most effective malaria vaccine candidate to date, demonstrated 56% efficacy over 12 months in African children. We therefore assessed a new candidate vaccine for safety and efficacy.
Methods: In this double-blind, randomised, controlled, phase 2b trial, the low-dose circumsporozoite protein-based vaccine R21, with two different doses of adjuvant Matrix-M (MM), was given to children aged 5-17 months in Nanoro, Burkina Faso-a highly seasonal malaria transmission setting. Three vaccinations were administered at 4-week intervals before the malaria season, with a fourth dose 1 year later. All vaccines were administered intramuscularly into the thigh. Group 1 received 5 µg R21 plus 25 µg MM, group 2 received 5 µg R21 plus 50 µg MM, and group 3, the control group, received rabies vaccinations. Children were randomly assigned (1:1:1) to groups 1-3. An independent statistician generated a random allocation list, using block randomisation with variable block sizes, which was used to assign participants. Participants, their families, and the local study team were all masked to group allocation. Only the pharmacists preparing the vaccine were unmasked to group allocation. Vaccine safety, immunogenicity, and efficacy were evaluated over 1 year. The primary objective assessed protective efficacy of R21 plus MM (R21/MM) from 14 days after the third vaccination to 6 months. Primary analyses of vaccine efficacy were based on a modified intention-to-treat population, which included all participants who received three vaccinations, allowing for inclusion of participants who received the wrong vaccine at any timepoint. This trial is registered with ClinicalTrials.gov, NCT03896724.
Findings: From May 7 to June 13, 2019, 498 children aged 5-17 months were screened, and 48 were excluded. 450 children were enrolled and received at least one vaccination. 150 children were allocated to group 1, 150 children were allocated to group 2, and 150 children were allocated to group 3. The final vaccination of the primary series was administered on Aug 7, 2019. R21/MM had a favourable safety profile and was well tolerated. The majority of adverse events were mild, with the most common event being fever. None of the seven serious adverse events were attributed to the vaccine. At the 6-month primary efficacy analysis, 43 (29%) of 146 participants in group 1, 38 (26%) of 146 participants in group 2, and 105 (71%) of 147 participants in group 3 developed clinical malaria. Vaccine efficacy was 74% (95% CI 63-82) in group 1 and 77% (67-84) in group 2 at 6 months. At 1 year, vaccine efficacy remained high, at 77% (67-84) in group 1. Participants vaccinated with R21/MM showed high titres of malaria-specific anti-Asn-Ala-Asn-Pro (NANP) antibodies 28 days after the third vaccination, which were almost doubled with the higher adjuvant dose. Titres waned but were boosted to levels similar to peak titres after the primary series of vaccinations after a fourth dose administered 1 year later.
Interpretation: R21/MM appears safe and very immunogenic in African children, and shows promising high-level efficacy.

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Safety, Tolerability, and Immunogenicity of Plasmodium falciparum Sporozoite Vaccine Administered by Direct Venous Inoculation to Infants and Young Children: Findings From an Age De-escalation, Dose-Escalation, Double-blind, Randomized Controlled Study in Western Kenya

Laura C Steinhardt[1], Thomas L Richie[2], Reuben Yego[3], Dorcas Akach[3], Mary J Hamel[1], Julie R Gutman[1], Ryan E Wiegand[1], Elizabeth L Nzuu[3], Allan Dungani[3], Natasha Kc[2], Tooba Murshedkar[2], L W Preston Church[2], B Kim Lee Sim[2], Peter F Billingsley[2], Eric R James[2], Yonas Abebe[2], Simon Kariuki[3], Aaron M Samuels[1], Kephas Otieno[3], Tony Sang[3], S Patrick Kachur[1,4], David Styers[5], Kelly Schlessman[5], Ginnie Abarbanell[6], Stephen L Hoffman[2], Robert A Seder[7], Martina Oneko[3]

Abstract

Background: The whole Plasmodium falciparum sporozoite (PfSPZ) vaccine is being evaluated for malaria prevention. The vaccine is administered intravenously for maximal efficacy. Direct venous inoculation (DVI) with PfSPZ vaccine has been safe, tolerable, and feasible in adults, but safety data for children and infants are limited.

Methods: We conducted an age de-escalation, dose-escalation randomized controlled trial in Siaya County, western Kenya. Children and infants (aged 5-9 years, 13-59 months, and 5-12 months) were enrolled into 13 age-dose cohorts of 12 participants and randomized 2:1 to vaccine or normal saline placebo in escalating doses: 1.35 × 105, 2.7 × 105, 4.5 × 105, 9.0 × 105, and 1.8 × 106 PfSPZ, with the 2 highest doses given twice, 8 weeks apart. Solicited adverse events (AEs) were monitored for 8 days after vaccination, unsolicited AEs for 29 days, and serious AEs throughout the study. Blood taken prevaccination and 1 week postvaccination was tested for immunoglobulin G antibodies to P. falciparum circumsporozoite protein (PfCSP) using enzyme-linked immunosorbent assay.

Results: Rates of AEs were similar in vaccinees and controls for solicited (35.7% vs 41.5%) and unsolicited (83.9% vs 92.5%) AEs, respectively. No related grade 3 AEs, serious AEs, or grade 3 laboratory abnormalities occurred. Most (79.0%) vaccinations were administered by a single DVI. Among those in the 9.0 × 105 and 1.8 × 106 PfSPZ groups, 36 of 45 (80.0%) vaccinees and 4 of 21 (19.0%) placebo controls developed antibodies to PfCSP (P < .001).

Conclusions: PfSPZ vaccine in doses as high as 1.8 × 106 can be administered to infants and children by DVI, and was safe, well tolerated, and immunogenic.

Measles vaccine

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Reduction in Short-term Outpatient Consultations After a Campaign With Measles Vaccine in Children Aged 9-59 Months: Substudy Within a Cluster-Randomized Trial

Anshu Varma[1,2,3], Peter Aaby[1,2,3], Sanne Marie Thysen[1,2,3], Aksel Karl Georg Jensen[1,3,4], Ane Bærent Fisker[1,2,3]

Abstract

Background: We assessed a measles vaccination campaign's potential short-term adverse events.

Methods: In a cluster-randomized trial assessing a measles vaccination campaign's effect on all-cause mortality and hospital admission among children aged 9-59 months in Guinea-Bissau, children received a measles vaccination (intervention) or a health check-up (control). One month to 2 months later, we visited a subgroup of children to ask mothers/guardians

about outpatient consultations since enrollment. In log-binomial models, we estimated the relative risk (RR) of nonaccidental outpatient consultations.
Results: Among 8319 children (4437 intervention/3882 control), 652 nonaccidental outpatient consultations occurred (322 intervention/330 control). The measles vaccination campaign tended to reduce nonaccidental outpatient consultations by 16% (RR, 0.84 [95% confidence interval {CI}, .65-1.11]), especially if caused by respiratory symptoms (RR, 0.68 [95% CI, .42-1.11]). The reduction tended to be larger in children who prior to trial enrollment had a pentavalent vaccination (diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b) as the most recent vaccination (RR, 0.61 [95% CI, .42-.89]) than in children who prior to trial enrollment had a routine measles vaccination as the most recent vaccination (RR, 0.93 [95% CI, .68-1.26]) (P = .04 for interaction).
Conclusions: In the short term, a measles vaccination campaign seems not to increase nonaccidental outpatient consultations but may reduce them.

Measles, mumps, rubella (MMR) vaccine

Meningococcal vaccine

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Meningococcal Serogroup ACWYX Conjugate Vaccine in Malian Toddlers
Milagritos D Tapia[1], Samba O Sow[1], Abdi Naficy[1], Fatoumata Diallo[1], Fadima C Haidara[1], Amol Chaudhari[1], Lionel Martellet[1], Awa Traore[1], Kelly Townsend-Payne[1], Ray Borrow[1], Nancy Hosken[1], Igor Smolenov[1], Sambhaji S Pisal[1], F Marc LaForce[1], Rajeev M Dhere[1], Dhananjay Kapse[1], Yuxiao Tang[1], Mark R Alderson[1], Prasad S Kulkarni[1]
Abstract
Background: *Neisseria meningitidis* serogroups A, B, C, W, X, and Y cause outbreaks of meningococcal disease. Quadrivalent conjugate vaccines targeting the A, C, W, and Y serogroups are available. A pentavalent vaccine that also includes serogroup X (NmCV-5) is under development.
Methods: We conducted a phase 2, observer-blinded, randomized, controlled trial involving Malian children 12 to 16 months of age. Participants were assigned in a 2:2:1 ratio to receive nonadjuvanted NmCV-5, alum-adjuvanted NmCV-5, or the quadrivalent vaccine MenACWY-D, administered intramuscularly in two doses 12 weeks apart. Participants were followed for safety for 169 days. Immunogenicity was assessed with an assay for serum bactericidal antibody (SBA) with rabbit complement on days 0, 28, 84, and 112.
Results: A total of 376 participants underwent randomization, with 150 assigned to each NmCV-5 group and 76 to the MenACWY-D group; 362 participants received both doses of vaccine. A total of 1% of the participants in the nonadjuvanted NmCV-5 group, 1% of those in the adjuvanted NmCV-5 group, and 4% of those in the MenACWY-D group reported local solicited adverse events; 6%, 5%, and 7% of the participants, respectively, reported systemic solicited adverse events. An SBA titer of at least 128 was seen in 91 to 100% (for all five serotypes) of the participants in the NmCV-5 groups and in 36 to 99% (excluding serogroup X) of those in the MenACWY-D group at day 84 (before the second dose); the same threshold was met in 99 to 100% (for all five serotypes) of the participants in the NmCV-5 groups and in

92 to 100% (excluding serogroup X) of those in the MenACWY-D group at day 112. Immune responses to the nonadjuvanted and adjuvanted NmCV-5 formulations were similar.
Conclusions: No safety concerns were identified with two doses of NmCV-5. A single dose of NmCV-5 elicited immune responses that were similar to those observed with two doses of MenACWY-D. Adjuvanted NmCV-5 provided no discernible benefit over nonadjuvanted NmCV-5.

Pneumococcal vaccine

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Immunogenicity of alternative ten-valent pneumococcal conjugate vaccine schedules in infants in Ho Chi Minh City, Vietnam: results from a single-blind, parallel-group, open-label, randomised, controlled trial
Paul Vincent Licciardi[1], Beth Temple[2], Vo Thi Trang Dai[3], Nguyen Trong Toan[4], Doan Uyen[4], Cattram Duong Nguyen[1], Thanh V Phan[3], Kathryn Bright[5], Rachel Ann Marimla[5], Anne Balloch[5], Tran Ngoc Huu[4], Kim Mulholland[6]
Abstract
Background: Data are scarce from low-income and middle-income countries (LMICs) to support the choice of vaccination schedule for the introduction of pneumococcal conjugate vaccines (PCV). We aimed to compare the immunogenicity of four different infant PCV10 schedules in infants in Vietnam.
Methods: In this single-blind, parallel-group, open-label, randomised controlled trial, infants aged 2 months were recruited by community health staff in districts 4 and 7 of Ho Chi Minh City, Vietnam. Eligible infants had no clinically significant maternal or prenatal history and were born at or after 36 weeks' gestation. Participants were randomly assigned (3:3:5:4:5:4) using block randomisation, stratified by district, to one of six PCV10 or PCV13 vaccination schedules. Here we report results for four groups: group A, who were given PCV10 at ages 2, 3, 4, and 9 months (a 3 + 1 schedule); group B, who were vaccinated at ages 2, 3, and 4 months (3 + 0 schedule); group C, who were vaccinated at ages 2, 4, and 9·5 months (2 + 1 schedule); and group D, who were vaccinated at ages 2 and 6 months (two-dose schedule). Laboratory-based assessors were masked to group allocation. Blood samples were collected at different prespecified timepoints between ages 3-18 months depending on group allocation, within 27-43 days after vaccination, and these were analysed for serotype-specific IgG and opsonophagocytic responses. Participants were followed-up until age 24 months. The primary outcome was the proportion of infants with serotype-specific IgG levels of 0·35 µg/mL or higher at age 5 months, analysed as a non-inferiority comparison (10% margin) of the two-dose and three-dose primary series (group C vs groups A and B combined). We also compared responses 4 weeks after two doses administered at either ages 2 and 4 months (group C) or at ages 2 and 6 months (group D). The primary endpoint was analysed in the per-protocol population. Reactogenicity has been reported previously. This study is registered with ClinicalTrials.gov, NCT01953510, and is now closed to accrual.
Findings: Between Sept 30, 2013, and Jan 9, 2015, 1201 infants were enrolled and randomly assigned to group A (n=152), group B (n=149), group C (n=250), group D (n=202), or groups E

(n=251) and F (n=197). In groups A-D, 388 (52%) of 753 participants were female and 365 (48%) were male. 286 (95%) participants in groups A and B combined (three-dose primary series) and 237 (95%) in group C (two-dose primary series) completed the primary vaccination series and had blood samples taken within the specified time window at age 5 months (per-protocol population). At this timepoint, a two-dose primary series was non-inferior to a three-dose primary series for eight of ten vaccine serotypes; exceptions were 6B (84·6% [95% CI 79·9-88·6] of infants had protective IgG concentrations after three doses [groups A and B combined] vs 76·8% [70·9-82·0] of infants after two doses [group C]; risk difference 7·8% [90% CI 2·1-13·6]) and 23F (90·6% [95% CI 86·6-93·7] vs 77·6% [71·8-82·2]; 12·9% [90% CI 7·7-18·3]). Two doses at ages 2 and 6 months produced higher antibody levels than two doses at ages 2 and 4 months for all serotypes except 5 and 7F.
Interpretation: A two-dose primary vaccination series was non-inferior to a three-dose primary vaccination series while two doses given with a wider interval between doses increased immunogenicity. The use of a two-dose primary vaccination schedule using a wider interval could be considered in LMIC settings to extend protection in the second year of life.

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Safety, immunogenicity, and transplacental antibody transport of conjugated and polysaccharide pneumococcal vaccines administered to pregnant women with HIV: a multicentre randomised controlled trial
Adriana Weinberg[1], Petronella Muresan[2], Lauren Laimon[3], Stephen I Pelton[4], David Goldblatt[5], Jennifer Canniff[6], Bonnie Zimmer[7], Frederic Bone[7], Lassallete Newton[3], Terence Fenton[2], James Kiely[8], Michael J Johnson[6], Esau C Joao[9], Breno R Santos[10], Elizabeth S Machado[11], Jorge A Pinto[12], Nahida Chakhtoura[13], Geraldo Duarte[14], Marisa M Mussi-Pinhata[14], NICHD P1091 study team
Abstract
Background: Pneumococcus remains an important cause of morbidity in pregnant women with HIV and their infants. We compared the safety and immunogenicity of PCV-10 and PPV-23 with placebo administered in pregnancy.
Methods: This double-blind, multicentre, randomised controlled trial was done at eight outpatient clinics in Brazil. Eligible participants were adult women with HIV who were pregnant at a gestational age between 14 weeks and less than 34 weeks and who were taking antiretroviral therapy at study entry. Participants were randomly assigned (1:1:1) to receive either PCV-10, PPV-23, or placebo. Participants and study teams were unaware of treatment allocation. Antibodies against seven vaccine serotypes in PCV-10 and PPV-23 were measured by ELISA. The primary outcomes were maternal and infant safety assessed by the frequency of adverse events of grade 3 or higher; maternal seroresponse (defined as ≥2-fold increase in antibodies from baseline to 28 days after immunisation) against five or more serotypes; and infant seroprotection (defined as anti-pneumococcus antibody concentration of ≥0·35 µg/mL) against five or more serotypes at 8 weeks of life. The study was powered to detect

differences of 20% or higher in the primary immunological outcomes between treatment groups. This trial is registered with ClinicalTrials.gov, NCT02717494.
Findings: Between April 1, 2016, and Nov 30, 2017, we enrolled 347 pregnant women with HIV, of whom 116 were randomly assigned to the PCV-10 group, 115 to the PPV-23 group, and 116 to the placebo group. One participant in the PCV-10 group did not receive the vaccine and was excluded from subsequent analyses. The frequency of adverse events of grade 3 or higher during the first 4 weeks was similar in the vaccine and placebo groups (3% [90% CI 1-7] for the PCV-10 group, 2% [0-5] for the PPV-23 group, and 3% [1-8] for the placebo group). However, injection site and systemic grade 2 adverse reactions were reported more frequently during the first 4 weeks in the vaccine groups than in the placebo group (14% [9-20] for the PCV-10 group, 7% [4-12] for the PPV-23 group, and 3% [1-7] for the placebo group). The frequency of grade 3 or higher adverse effects was similar across maternal treatment groups (20% [14-27] for the PCV-10 group, 21% [14-28] for the PPV-23 group, and 20% [14-27] for the placebo group). Seroresponses against five or more serotypes were present in 74 (65%) of 114 women in the PCV-10 group, 72 (65%) of 110 women in the PPV-23 group, and none of the 113 women in the placebo group at 4 weeks post vaccination (p<0·0001 for PPV-23 group vs placebo and PCV-10 group vs placebo). Seroresponse differences of 20% or higher in vaccine compared with placebo recipients persisted up to 24 weeks post partum. At birth, 76 (67%) of 113 infants in the PCV-10 group, 62 (57%) of 109 infants in the PPV-23 group, and 19 (17%) of 115 infants in the placebo group had seroprotection against five or more serotypes (p<0·0001 for PPV-23 vs placebo and PCV-10 vs placebo). At 8 weeks, the outcome was met by 20 (19%) of 108 infants in the PCV-10 group, 24 (23%) of 104 infants in the PPV-23 group, and one (1%) of 109 infants in the placebo group (p<0·0001). Although a difference of 20% or higher compared with placebo was observed only in the infants who received PPV-23 at 8 weeks of life, the difference between the two vaccine groups was not appreciable.
Interpretation: PCV-10 and PPV-23 were equally safe and immunogenic in pregnant women with HIV and conferred similar levels of seroprotection to their infants. In areas in which childhood PCV administration decreased the circulation of PCV serotypes, PPV-23 administration to pregnant women with HIV might be more advantageous than PCV by virtue of including a broader range of serotypes.

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doi: 10.1016/S1473-3099(20)30289-9. Epub 2020 Aug 25.
Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial
Shabir A Madhi[1], Eleonora Aml Mutsaerts[2], Alane Izu[2], Welekazi Boyce[2], Sutika Bhikha[2], Benit T Ikulinda[2], Lisa Jose[2], Anthonet Koen[2], Amit J Nana[2], Andrew Moultrie[2], Lucy Roalfe[3], Adam Hunt[3], David Goldblatt[3], Clare L Cutland[2], Jeffrey R Dorfman[2]
Abstract
Background: Routine childhood immunisation with pneumococcal conjugate vaccine (PCV) has changed the epidemiology of pneumococcal disease across age groups, providing an opportunity to reconsider PCV dosing schedules. We aimed to evaluate the post-booster

dose immunogenicity of ten-valent (PCV10) and 13-valent (PCV13) PCVs between infants randomly assigned to receive a single-dose compared with a two-dose primary series.
Methods: We did an open-label, non-inferiority, randomised study in HIV-unexposed infants at a single centre in Soweto, South Africa. Infants were randomly assigned to receive one priming dose of PCV10 or PCV13 at ages 6 weeks (6w + 1 PCV10 and 6w + 1 PCV13 groups) or 14 weeks (14w + 1 PCV10 and 14w + 1 PCV13 groups) or two priming doses of PCV10 or PCV13, one each at ages 6 weeks and 14 weeks (2 + 1 PCV10 and 2 + 1 PCV13 groups); all participants then received a booster dose of PCV10 or PCV13 at 40 weeks of age. The primary endpoint was geometric mean concentrations (GMCs) of serotype-specific IgG 1 month after the booster dose, which was assessed in all participants who received PCV10 or PCV13 as per the assigned randomisation group and for whom laboratory results were available at that timepoint. The 1 + 1 vaccine schedule was considered non-inferior to the 2 + 1 vaccine schedule if the lower bound of the 96% CI for the GMC ratio was greater than 0·5 for at least ten PCV13 serotypes and eight PCV10 serotypes. Safety was a secondary endpoint. This trial is registered with ClinicalTrials.gov (NCT02943902) and is ongoing.
Findings: Of 1695 children assessed, 600 were enrolled and randomly assigned to one of the six groups between Jan 9 and Sept 20, 2017; 542 were included in the final analysis of the primary endpoint (86-93 per group). For both PCV13 and PCV10, a 1+1 dosing schedule (either beginning at 6 or 14 weeks) was non-inferior to a 2 + 1 schedule. For PCV13, the lower limit of the 96% CI for the ratio of GMCs between the 1 + 1 and 2 + 1 groups was higher than 0·5 for ten serotypes in the 6w+1 group (excluding 6B, 14, and 23F) and 11 serotypes in the 14w + 1 group (excluding 6B and 23F). For PCV10, the lower limit of the 96% CI for the ratio of GMCs was higher than 0·5 for all ten serotypes in the 6w+1 and 14w + 1 groups. 84 serious adverse events were reported in 72 (12%) of 600 participants. 15 occurred within 28 days of vaccination, but none were considered to be related to PCV injection. There were no cases of culture-confirmed invasive pneumococcal disease.
Interpretation: The non-inferiority in post-booster immune responses following a single-dose compared with a two-dose primary series of PCV13 or PCV10 indicates the potential for reducing PCV dosing schedules from a 2 + 1 to 1 + 1 series in low-income and middle-income settings with well established PCV immunisation programmes.

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Bacterial nasopharyngeal carriage following infant immunization with pneumococcal conjugate vaccines according to a 2+1 schedule in children in South Africa: an exploratory analysis of two clinical trials

Marta C Nunes[1,2], Marta Moreira[3], Anthonet Koen[1,2], Nadia van Niekerk[1,2], Lisa Jose[1,2], Clare L Cutland[1,2], Nancy François[3], Sonia Schoonbroodt[3], Javier Ruiz-Guiñazú[3], Juan Pablo Yarzabal[3], Dorota Borys[3], Lode Schuerman[3], Shabir A Madhi[1,2]

Abstract
Background: We evaluated bacterial nasopharyngeal carriage (NPC) prevalence and cumulative acquisition following 7-valent pneumococcal conjugate vaccine (PCV7) or pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) administration. **Methods**: Participants were children from two clinical trials in a South

African center who received PCV7 (n = 250) or PHiD-CV (n = 100) at ~6 weeks, ~14 weeks, and ~9-10 months of age, and were enrolled between Dec2009-Apr2010 and Mar2009-May2010 in the PCV7 and PHiD-CV studies, respectively. Sample collection, most microbiological assessments, and data re-analysis methods were identical. **Results**: NPC prevalence of any pneumococcal serotype was 18.5% and 17.0% at pre-vaccination, and 63.1% and 67.3% in 24-27 month-old children among PCV7 and PHiD-CV recipients, respectively. In 24-27 month-old children, 96.1% and 99.0% of PCV7 and PHiD-CV recipients had acquired ≥1 pneumococcal serotype, 53.7% and 62.9% ≥1 PCV7 serotype, 1.5%, and 3.1% ≥1 of serotypes 1, 5 or 7F, 23.2% and 19.6% serotype 6A, 23.2% and 21.7% serotype 19A, 88.7%, and 91.0% *H. influenzae*, and 50.3% and 62.9% *Staphylococcus aureus*, respectively. **Conclusions**: This analysis of two concurrent clinical trials did not reveal differences in bacterial NPC prevalence or acquisition in PCV7- and PHiD-CV-vaccinated children.

Polio vaccine

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Safety and immunogenicity of two novel type 2 oral poliovirus vaccine candidates compared with a monovalent type 2 oral poliovirus vaccine in children and infants: two clinical trials

Xavier Sáez-Llorens[1], Ananda S Bandyopadhyay[2], Christopher Gast[3], Tirza De Leon[4], Rodrigo DeAntonio[5], Jose Jimeno[6], Maria Isabel Caballero[6], Gabriela Aguirre[7], M Steven Oberste[8], William C Weldon[8], Jennifer L Konopka-Anstadt[8], John Modlin[9], Novilia S Bachtiar[10], Alan Fix[3], John Konz[3], Ralf Clemens[11], Sue Ann Costa Clemens[12], Ricardo Rüttimann[13]

Abstract

Background: Continued emergence and spread of circulating vaccine-derived type 2 polioviruses and vaccine-associated paralytic poliomyelitis from Sabin oral poliovirus vaccines (OPVs) has stimulated development of two novel type 2 OPV candidates (OPV2-c1 and OPV2-c2) designed to have similar immunogenicity, improved genetic stability, and less potential to reacquire neurovirulence. We aimed to assess safety and immunogenicity of the two novel OPV candidates compared with a monovalent Sabin OPV in children and infants.

Methods: We did two single-centre, multi-site, partly-masked, randomised trials in healthy cohorts of children (aged 1-4 years) and infants (aged 18-22 weeks) in Panama: a control phase 4 study with monovalent Sabin OPV2 before global cessation of monovalent OPV2 use, and a phase 2 study with low and high doses of two novel OPV2 candidates. All participants received one OPV2 vaccination and subsets received two doses 28 days apart. Parents reported solicited and unsolicited adverse events. Type 2 poliovirus neutralising antibodies were measured at days 0, 7, 28, and 56, and stool viral shedding was assessed up to 28 days post-vaccination. Primary objectives were to assess safety in all participants and non-inferiority of novel OPV2 day 28 seroprotection versus monovalent OPV2 in infants (non-inferiority margin 10%).

Findings: The control study took place between Oct 23, 2015, and April 29, 2016, and the subsequent phase 2 study between Sept 19, 2018, and Sept 30, 2019. 150 children (50 in the

control study and 100 of 129 assessed for eligibility in the novel OPV2 study) and 684 infants (110 of 114 assessed for eligibility in the control study and 574 of 684 assessed for eligibility in the novel OPV2 study) were enrolled and received at least one study vaccination. Vaccinations were safe and well tolerated with no causally associated serious adverse events or important medical events in any group. Solicited and unsolicited adverse events were overwhelmingly mild or moderate irrespective of vaccine or dose. Nearly all children were seroprotected at baseline, indicating high baseline immunity. In children, the seroprotection rate 28 days after one dose was 100% for monovalent OPV2 and both novel OPV2 candidates. In infants at day 28, 91 (94% [95% CI 87-98]) of 97 were seroprotected after receiving monovalent OPV2, 134 (94% [88-97]) of 143 after high-dose novel OPV2-c1, 122 (93% [87-97]) of 131 after low-dose novel OPV2-c1, 138 (95% [90-98]) of 146 after high-dose novel OPV2-c2, and 115 (91% [84-95]) of 127 after low-dose novel OPV2-c2. Non-inferiority was shown for low-dose and high-dose novel OPV2-c1 and high-dose novel OPV2-c2 despite monovalent OPV2 recipients having higher baseline immunity.
Interpretation: Both novel OPV2 candidates were safe, well tolerated, and immunogenic in children and infants. Novel OPV2 could be an important addition to our resources against poliovirus given the current epidemiological situation.

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Randomized Controlled Clinical Trial of bivalent Oral Poliovirus Vaccine and Inactivated Poliovirus Vaccine in Nigerian Children
Beckie N Tagbo[1], Harish Verma[2], Zubairu M Mahmud[3], Kolade Ernest[4], Roosevelt O Nnani[5], Chinedu Chukwubike[5], Kehinde T Craig[6], Abdullahi Hamisu[6], William C Weldon[7], Steven M Oberste[7], Visalakshi Jeyaseelan[2], Fiona Braka[6], Pascal Mkanda[8], Dorothy Esangbedo[9], Adebiyi Olowu[9], Eric Nwaze[10], Roland W Sutter[2]
Abstract
Background: We conducted a trial in Nigeria to assess the immunogenicity of the new bOPV + IPV immunization schedule and gains in type 2 immunity with addition of second dose of IPV. The trial was conducted in August 2016-March 2017 period, well past the tOPV-bOPV switch in April 2016.
Methods: This was an open-label, two-arm, non-inferiority, multi-center, randomized controlled trial. We enrolled 572 infants of age ≤14 days and randomized them into two arms. Arm A received bOPV at birth, 6 and 10 weeks, bOPV+IPV at week 14 and IPV at week 18. Arm B received IPV each at 6, 10, 14 weeks and bOPV at 18 weeks of age.
Results: Seroconversion rates for poliovirus types 1 and 3, respectively, were 98.9% (95%CI:96.7-99.8) and 98.1% (95%CI:88.2-94.8) in Arm A, and 89.6% (95%CI:85.4-93.0) and 98.5% (95%CI:96.3-99.6) in Arm B. Type 2 seroconversion with one dose IPV in Arm A was 72.0% (95%CI:66.2-77.3), which increased significantly with addition of second dose to 95.9% (95%CI:92.8-97.9).
Conclusion: This first trial on the new EPI schedule in a sub-Saharan African country demonstrated excellent immunogenicity against poliovirus types 1 and 3, and substantial/enhanced immunogenicity against poliovirus type 2 after 1 to 2 doses of IPV respectively.

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Safety and immunogenicity of inactivated poliovirus vaccine schedules for the post-eradication era: a randomised open-label, multicentre, phase 3, non-inferiority trial

Ananda S Bandyopadhyay[1], Chris Gast[2], Luis Rivera[3], Xavier Sáez-Llorens[4], M Steven Oberste[5], William C Weldon[5], John Modlin[6], Ralf Clemens[7], Sue Ann Costa Clemens[7], Jose Jimeno[4], Ricardo Rüttimann[8]

Abstract

Background: Following the global eradication of wild poliovirus, countries using live attenuated oral poliovirus vaccines will transition to exclusive use of inactivated poliovirus vaccine (IPV) or fractional doses of IPV (f-IPV; a f-IPV dose is one-fifth of a normal IPV dose), but IPV supply and cost constraints will necessitate dose-sparing strategies. We compared immunisation schedules of f-IPV and IPV to inform the choice of optimal post-eradication schedule.

Methods: This randomised open-label, multicentre, phase 3, non-inferiority trial was done at two centres in Panama and one in the Dominican Republic. Eligible participants were healthy 6-week-old infants with no signs of febrile illness or known allergy to vaccine components. Infants were randomly assigned (1:1:1:1, 1:1:1:2, 2:1:1:1), using computer-generated blocks of four or five until the groups were full, to one of four groups and received: two doses of intradermal f-IPV (administered at 14 and 36 weeks; two f-IPV group); or three doses of intradermal f-IPV (administered at 10, 14, and 36 weeks; three f-IPV group); or two doses of intramuscular IPV (administered at 14 and 36 weeks; two IPV group); or three doses of intramuscular IPV (administered at 10, 14, and 36 weeks; three IPV group). The primary outcome was seroconversion rates based on neutralising antibodies for poliovirus type 1 and type 2 at baseline and at 40 weeks (4 weeks after the second or third vaccinations) in the per-protocol population to allow non-inferiority and eventually superiority comparisons between vaccines and regimens. Three co-primary outcomes concerning poliovirus types 1 and 2 were to determine if seroconversion rates at 40 weeks of age after a two-dose regimen (administered at weeks 14 and 36) of intradermally administered f-IPV were non-inferior to a corresponding two-dose regimen of intramuscular IPV; if seroconversion rates at 40 weeks of age after a two-dose IPV regimen (weeks 14 and 36) were non-inferior to those after a three-dose IPV regimen (weeks 10, 14, and 36); and if seroconversion rates after a two-dose f-IPV regimen (weeks 14 and 36) were non-inferior to those after a three-dose f-IPV regimen (weeks 10, 14, and 36). The non-inferiority boundary was set at -10% for the lower bound of the two-sided 95% CI for the seroconversion rate difference.. Safety was assessed as serious adverse events and important medical events. This study is registered on ClinicalTrials.gov, NCT03239496.

Findings: From Oct 23, 2017, to Nov 13, 2018, we enrolled 773 infants (372 [48%] girls) in Panama and the Dominican Republic (two f-IPV group n=217, three f-IPV group n=178, two IPV group n=178, and three IPV group n=200). 686 infants received all scheduled vaccine doses and were included in the per-protocol analysis. We observed non-inferiority for poliovirus type 1 seroconversion rate at 40 weeks for the two f-IPV dose schedule (95·9% [95% CI 92·0-98·2]) versus the two IPV dose schedule (98·7% [95·4-99·8]), and for the three f-IPV dose schedule (98·8% [95·6-99·8]) versus the three IPV dose schedule (100% [97·9-100]). Similarly, poliovirus type 2 seroconversion rate at 40 weeks for the two f-IPV dose schedule (97·9% [94·8-99·4]) versus the two IPV dose schedule (99·4% [96·4-100]), and for the three f-IPV dose schedule (100% [97·7-100]) versus the three IPV dose schedule (100% [97·9-100])

were non-inferior. Seroconversion rate for the two f-IPV regimen was statistically superior 4 weeks after the last vaccine dose in the 14 and 36 week schedule (95·9% [92·0-98·2]) compared with the 10 and 14 week schedule (83·2% [76·5-88·6]; p=0·0062) for poliovirus type 1. Statistical superiority of the 14 and 36 week schedule was also found for poliovirus type 2 (14 and 36 week schedule 97·9% [94·8-99·4] vs 10 and 14 week schedule 83·9% [77·2-89·2]; p=0·0062), and poliovirus type 3 (14 and 36 week schedule 84·5% [78·7-89·3] vs 10 and 14 week schedule 73·3% [65·8-79·9]; p=0·0062). For IPV, a two dose regimen administered at 14 and 36 weeks (99·4% [96·4-100]) was superior a 10 and 14 week schedule (88·9% [83·4-93·1]; p<0·0001) for poliovirus type 2, but not for type 1 (14 and 36 week schedule 98·7% [95·4-99·8] vs 10 and 14 week schedule 95·6% [91·4-98·1]), or type 3 (14 and 36 week schedule 97·4% [93·5-99·3] vs 10 and 14 week schedule 93·9% [89·3-96·9]). There were no related serious adverse events or important medical events reported in any group showing safety was unaffected by administration route or schedule.

Interpretation: Our observations suggest that adequate immunity against poliovirus type 1 and type 2 is provided by two doses of either IPV or f-IPV at 14 and 36 weeks of age, and broad immunity is provided with three doses of f-IPV, enabling substantial savings in cost and supply. These novel clinical data will inform global polio immunisation policy for the post-eradication era.

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Immunogenicity and safety of different sequential schedules of Sabin strain-based inactivated poliovirus vaccination: A randomized, controlled, open-label, phase IV clinical trial in China

Shaohong Yan[1], Haiping Chen[2], Zhenguo Zhang[3], Shaoying Chang[4], Yanhui Xiao[2], Linyun Luo[2], Zhaoyong Zhang[1], Li Sun[3], Xiao Chen[4], Yunkai Yang[5], Xuanwen Shi[2], Yu Guo[1], Yunlong Sun[3], Hong Li[4], Na Li[5], Shasha Han[2], Meng Ma[5], Xiaoming Yang[6]

Abstract

Background: The immunogenicity and safety of the sequential schedule of Sabin strain-based inactivated poliovirus vaccine (sIPV) and bivalent oral poliovirus vaccine (bOPV) remains poorly understood in Chinese population.

Methods: A multi-center, open-label, randomized controlled trial was performed involving 648 healthy infants aged 2 months from Inner Mongolia, Shanxi, and Hebei provinces. These participants were divided into three groups: sIPV-bOPV-bOPV, sIPV-sIPV-bOPV, and sIPV-sIPV-sIPV. Doses were administered sequentially at age 2, 3, and 4 months. Neutralisation assays were tested using sera collected at 2 months and 5 months.

Results: A total of 569 were included in the per-protocol analysis. The seroconversion rates of poliovirus type 1 and 3 were 100% in all three groups, the seroconversion rate of poliovirus type 2 was 91.53% (173/189) (95% CI: 86.62-95.08) in the sIPV-bOPV-bOPV group, 98.38% (182/185) (95% CI: 95.33-99.66) in the sIPV-sIPV-bOPV group, and 99.49% (194/195) (95% CI: 97.18-99.99) in the sIPV-sIPV-sIPV group. For the seroconversion rate of poliovirus types 1 and 3, the sIPV-bOPV-bOPV and sIPV-sIPV-bOPV groups were non-inferior to the sIPV-sIPV-sIPV group. For the seroconversion rate of poliovirus type 2, the sIPV-sIPV-bOPV group was non-inferior to the sIPV-sIPV-sIPV group, and the sIPV-bOPV-bOPV group was inferior to the

sIPV-sIPV-sIPV group. All three groups exhibited good safety, with two serious adverse events reported, that were unrelated to vaccine.
Conclusions: In china, a new vaccination schedule that including 2 doses of IPV in the national immunization programs is essential.

Rotavirus vaccine

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doi: 10.12688/wellcomeopenres.16174.2. eCollection 2020.
Effectiveness of Rotarix ® vaccine in Africa in the first decade of progressive introduction, 2009-2019: systematic review and meta-analysis
Nickson Murunga[1,2], Grieven P Otieno[1], Marta Maia[1,3], Charles N Agoti[1,2]
Abstract
Background: Randomized controlled trials of licensed oral rotavirus group A (RVA) vaccines, indicated lower efficacy in developing countries compared to developed countries. We investigated the pooled effectiveness of Rotarix ® in Africa in 2019, a decade since progressive introduction began in 2009. **Methods:** A systematic search was conducted in PubMed to identify studies that investigated the effectiveness of routine RVA vaccination in an African country between 2009 and 2019. A meta-analysis was undertaken to estimate pooled effectiveness of the full-dose versus partial-dose of Rotarix ® (RV1) vaccine and in different age groups. Pooled odds ratios were estimated using random effects model and the risk of bias assessed using Newcastle-Ottawa scale. The quality of the evidence was assessed using GRADE. **Results:** By December 2019, 39 (72%) countries in Africa had introduced RVA vaccination, of which 34 were using RV1. Thirteen eligible studies from eight countries were included in meta-analysis for vaccine effectiveness (VE) of RVA by vaccine dosage (full or partial) and age categories. Pooled RV1 VE against RVA associated hospitalizations was 44% (95% confidence interval (CI) 28-57%) for partial dose versus 58% (95% CI 50-65%) for full dose. VE was 61% (95% CI 50-69%), 55% (95% CI 32-71%), 56% (95% CI 43-67%), and 61% (95% CI 42-73%) for children aged <12 months, 12-23 months, <24 months and 12-59 months, respectively. **Conclusion:** RV1 vaccine use has resulted in a significant reduction in severe diarrhoea in African children and its VE is close to the efficacy findings observed in clinical trials. RV1 VE point estimate was higher for children who received full dose than those who received partial dose, and its protection lasted beyond the first year of life.

RSV vaccine

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Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants

Shabir A Madhi[1], Fernando P Polack[1], Pedro A Piedra[1], Flor M Munoz[1], Adrian A Trenholme[1], Eric A F Simões[1], Geeta K Swamy[1], Sapeckshita Agrawal[1], Khatija Ahmed[1], Allison August[1], Abdullah H Baqui[1], Anna Calvert[1], Janice Chen[1], Iksung Cho[1], Mark F Cotton[1], Clare L Cutland[1], Janet A Englund[1], Amy Fix[1], Bernard Gonik[1], Laura Hammitt[1], Paul T Heath[1], Joanne N de Jesus[1], Christine E Jones[1], Asma Khalil[1], David W Kimberlin[1], Romina Libster[1], Conrado J Llapur[1], Marilla Lucero[1], Gonzalo Pérez Marc[1], Helen S Marshall[1], Masebole S Masenya[1], Federico Martinón-Torres[1], Jennifer K Meece[1], Terry M Nolan[1], Ayman Osman[1], Kirsten P Perrett[1], Joyce S Plested[1], Peter C Richmond[1], Matthew D Snape[1], Julie H Shakib[1], Vivek Shinde[1], Tanya Stoney[1], D Nigel Thomas[1], Alan T Tita[1], Michael W Varner[1], Manu Vatish[1], Keith Vrbicky[1], Judy Wen[1], Khalequ Zaman[1], Heather J Zar[1], Gregory M Glenn[1], Louis F Fries[1], Prepare Study Group

Free PMC article

Abstract

Background: Respiratory syncytial virus (RSV) is the dominant cause of severe lower respiratory tract infection in infants, with the most severe cases concentrated among younger infants.

Methods: Healthy pregnant women, at 28 weeks 0 days through 36 weeks 0 days of gestation, with an expected delivery date near the start of the RSV season, were randomly assigned in an overall ratio of approximately 2:1 to receive a single intramuscular dose of RSV fusion (F) protein nanoparticle vaccine or placebo. Infants were followed for 180 days to assess outcomes related to lower respiratory tract infection and for 364 days to assess safety. The primary end point was RSV-associated, medically significant lower respiratory tract infection up to 90 days of life, and the primary analysis of vaccine efficacy against the primary end point was performed in the per-protocol population of infants (prespecified criterion for success, lower bound of the 97.52% confidence interval [CI] of ≥30%).

Results: A total of 4636 women underwent randomization, and there were 4579 live births. During the first 90 days of life, the percentage of infants with RSV-associated, medically significant lower respiratory tract infection was 1.5% in the vaccine group and 2.4% in the placebo group (vaccine efficacy, 39.4%; 97.52% CI, -1.0 to 63.7; 95% CI, 5.3 to 61.2). The corresponding percentages for RSV-associated lower respiratory tract infection with severe hypoxemia were 0.5% and 1.0% (vaccine efficacy, 48.3%; 95% CI, -8.2 to 75.3), and the percentages for hospitalization for RSV-associated lower respiratory tract infection were 2.1% and 3.7% (vaccine efficacy, 44.4%; 95% CI, 19.6 to 61.5). Local injection-site reactions among the women were more common with vaccine than with placebo (40.7% vs. 9.9%), but the percentages of participants who had other adverse events were similar in the two groups.

Conclusions: RSV F protein nanoparticle vaccination in pregnant women did not meet the prespecified success criterion for efficacy against RSV-associated, medically significant lower respiratory tract infection in infants up to 90 days of life. The suggestion of a possible benefit with respect to other end-point events involving RSV-associated respiratory disease in infants warrants further study.

Salmonella typhi vaccine

Schistosomiasis vaccine

Tuberculosis vaccine

(also see Tuberculosis, Isoniazid preventative therapy)

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DAR-901 vaccine for the prevention of infection with Mycobacterium tuberculosis among BCG-immunized adolescents in Tanzania: A randomized controlled, double-blind phase 2b trial

Patricia Munseri[1], Jamila Said[1], Maryam Amour[1], Albert Magohe[1], Mecky Matee[1], Christiaan A Rees[2], Todd Mackenzie[2], Susan Tvaroha[1], Chris Bailey-Kellogg[2], Isaac Maro[3], Wendy Wieland-Alter[1], Lisa V Adams[2], C Robert Horsburgh[4], Keiko Nakamura[3], Robert D Arbeit[5], Kisali Pallangyo[1], C Fordham von Reyn[6]

Abstract

Background: SRL172 prevented disease due to Mycobacterium tuberculosis in a Phase 3 trial. DAR-901 represents a scalable manufacturing process for SRL172. We sought to determine if DAR-901 would prevent infection with M. tuberculosis among BCG-primed adolescents age 13-15 years in Tanzania.

Methods: Adolescents with a negative T- SPOT.TB^{R} interferon gamma release assay (IGRA) were randomized 1:1 to three intradermal injections of DAR-901 or saline placebo at 0, 2 and 4 months. Repeat IGRAs were performed at 2 months, and at 1, 2, and 3 years. The primary efficacy outcome was time to new TB infection (IGRA conversion to positive); the secondary outcome was time to persistent TB infection (IGRA conversion with repeat positive IGRA).

Results: Among 936 participants screened 667 were eligible and randomized to their first dose of vaccine or placebo (safety cohort). At 2 months, 625 participants remained IGRA-negative and were scheduled for the additional two doses (efficacy cohort). DAR-901 was safe and well-tolerated. One DAR-901 recipient developed a vaccine site abscess. Neither the primary nor secondary endpoints differed between the two treatment arms (p = 0.90 and p = 0.20, respectively). DAR-901 IGRA converters had median responses to ESAT-6 of 50.1 spot-forming cells (SFCs) vs. 19.6 SFCs in placebo IGRA converters (p = 0.03).

Conclusions: A three-dose series of 1 mg DAR-901 was safe and well-tolerated but did not prevent initial or persistent IGRA conversion. DAR-901 recipients with IGRA conversion demonstrated enhanced immune responses to ESAT-6. Since protection against disease may require different immunologic responses than protection against infection a trial of DAR-901 to prevent TB disease is warranted.

Typhoid vaccine

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Vi-specific serological correlates of protection for typhoid fever

Celina Jin[1,2], Jennifer Hill[1,2], Bronwyn M Gunn[3], Wen-Han Yu[3], Lindsay C Dahora[4], Elizabeth Jones[1,2], Mari Johnson[1,2], Malick M Gibani[1,2], Rachel L Spreng[4], S Munir Alam[4], Anna Nebykova[1,2], Helene B Juel[1,2], S Moses Dennison[4], Kelly E Seaton[4], Jonathan K Fallon[3], Georgia D Tomaras[4], Galit Alter[3], Andrew J Pollard[1,2]

Abstract

Typhoid Vi vaccines have been shown to be efficacious in children living in endemic regions; however, a widely accepted correlate of protection remains to be established. We applied a systems serology approach to identify Vi-specific serological correlates of protection using samples obtained from participants enrolled in an experimental controlled human infection study. Participants were vaccinated with Vi-tetanus toxoid conjugate (Vi-TT) or unconjugated Vi-polysaccharide (Vi-PS) vaccines and were subsequently challenged with Salmonella Typhi bacteria. Multivariate analyses identified distinct protective signatures for Vi-TT and Vi-PS vaccines in addition to shared features that predicted protection across both groups. Vi IgA quantity and avidity correlated with protection from S. Typhi infection, whereas higher fold increases in Vi IgG responses were associated with reduced disease severity. Targeted antibody-mediated functional responses, particularly neutrophil phagocytosis, were also identified as important components of the protective signature. These humoral markers could be used to evaluate and develop efficacious Vi-conjugate vaccines and assist with accelerating vaccine availability to typhoid-endemic regions.

Indian Pediatr. 2020 Jul 15;57(7):625-630.

Immunogenicity and Safety of Typhoid Conjugate Vaccine in Healthy Indian Subjects: A Randomized, Active-controlled, Comparative Clinical Trial

Ritabrata Kundu[1], Ambrose Kumar Kandulna[2], Uma Nayak[3], Sanjay Kumar Jangid[4], T Ramesh Babu[5], Rajesh Vukkala[6], Shrikant Sharma[7], Vimal Kant Goyal[8], Pavankumar Daultani[9], Ravindra Mittal[10], Pradip Patel[11]

Abstract

Objective: To compare the immunogenicity and safety of an investigational typhoid Vi conjugate vaccine (Test TCV) with a marketed typhoid Vi conjugate vaccine (Comparator TCV).

Design: Randomized, controlled trial.

Setting: Tertiary care and multispecialty hospitals.

Participants: 240 healthy subjects of 6 months to 45 years. Pediatric (<18 years) subjects were enrolled after day 21 safety assessment of adult subjects.

Intervention: Participants received a single-dose of test TCV or comparator TCV at baseline and were followed up for 6 weeks post-vaccination.

Main outcome measure: Primary variable was to demonstrate non-inferiority of the test TCV with the comparator TCV for seroconversion post-vaccination (^{3}4-fold rise in antibody titre). Secondary variables were seroconversion in the adult and pediatric cohorts, and geometric mean titre of antibodies while the safety was based on reported adverse events.

Results: A total of 117 subjects (Adult-58, Pediatric-59) and 119 subjects (Adult-60, Pediatric-59) in test and comparator group, respectively completed the study. The seroconversion rate with test TCV (overall-94.8%, adult-96.6% and pediatric-93.1%) was non-inferior to

comparator TCV (overall-91.6%, adult-91.7% and pediatric-91.5%). The geometric mean titres of antibodies (EU/mL) at baseline (test TCV: overall-7.6, adult-10.0, and pediatric-5.7; and comparator TCV: overall-8.0, adult-12.0, and pediatric-5.3) and at end of study (test TCV: overall-1121.0, adult-1411.0 and pediatric-891.1; and comparator TCV: overall-1104.0, adult-1199.0 and pediatric-1014.0) were also comparable between the groups (P>0.05 for all). The most common adverse event was injection-site pain followed by fever in both the groups.
Conclusions: The immunogenicity and safety of test TCV is comparable to already marketed comparator TCV.

Int J Infect Dis. 2021 Jan;102:517-523.
doi: 10.1016/j.ijid.2020.10.103. Epub 2020 Nov 8.

Safety and immunogenicity of co-administration of meningococcal type A and measles-rubella vaccines with typhoid conjugate vaccine in children aged 15-23 months in Burkina Faso

Sodiomon B Sirima[1], Alphonse Ouedraogo[1], Nouhoun Barry[1], Mohamadou Siribie[1], Alfred B Tiono[1], Issa Nébié[1], Amadou T Konaté[1], Gloria Damoaliga Berges[1], Amidou Diarra[1], Moussa Ouedraogo[1], Issiaka Soulama[1], Alimatou Hema[1], Shrimati Datta[2], Yuanyuan Liang[2], Elizabeth T Rotrosen[2], J Kathleen Tracy[2], Leslie P Jamka[2], Kathleen M Neuzil[2], Matthew B Laurens[3]

Abstract
Objectives: The World Health Organization pre-qualified single-dose typhoid conjugate vaccine (TCV) and requested data on co-administration with routine vaccines. The co-administration of Typbar TCV (Bharat Biotech International) with routine group A meningococcal conjugate vaccine (MCV-A) and measles-rubella (MR) vaccine was tested.
Methods: This was a double-blind, randomized controlled trial performed in Ouagadougou, Burkina Faso. Children were recruited at the 15-month vaccination visit and were assigned randomly (1:1:1) to three groups. Group 1 children received TCV plus control vaccine (inactivated polio vaccine) and MCV-A 28 days later; group 2 children received TCV and MCV-A; group 3 children received MCV-A and control vaccine. Routine MR vaccine was administered to all participants. Safety was assessed at 0, 3, and 7 days after immunization, and unsolicited adverse events and serious adverse events were assessed for 28 days and 6 months after immunization, respectively.
Results: A total of 150 children were recruited and vaccinated. Solicited symptoms were infrequent and similar for TCV and control recipients, as were adverse events (group 1, 61.2%; group 2, 64.0%; group 3, 68.6%) and serious adverse events (group 1, 2.0%; group 2, 8.0%; group 3, 5.9%). TCV generated robust immunity without interference with MCV-A vaccine.
Conclusions: TCV can be safely co-administered at 15 months with MCV-A without interference. This novel study on the co-administration of TCV with MCV-A provides data to support large-scale uptake in sub-Saharan Africa.

Varicella vaccine

Vitamin A

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doi: 10.1093/jn/nxaa439.

Small-Quantity Lipid-Based Nutrient Supplements Do Not Affect Plasma or Milk Retinol Concentrations Among Malawian Mothers, or Plasma Retinol Concentrations among Young Malawian or Ghanaian Children in Two Randomized Trials

Marjorie J Haskell[1,2], Rebecca Young[1,2], Seth Adu-Afaruwah[3], Anna Lartey[3], Harriet Eyram Teiko Okronipa[1,2,3], Kenneth Maleta[4], Ulla Ashorn[5], Josh M Jorgensen[1,2], Yue-Mei Fan[5], Charles D Arnold[1,2], Lindsay H Allen[1,2,6], Per Ashorn[5,7], Kathryn G Dewey[1,2]

Abstract

Background: Vitamin A (VA) deficiency is prevalent in preschool-aged children in sub-Saharan Africa.

Objectives: We assessed the effect of small-quantity lipid-based nutrient supplements (SQ-LNS) given to women during pregnancy and lactation and their children from 6 to 18 mo of age on women's plasma and milk retinol concentrations in Malawi, and children's plasma retinol concentration in Malawi and Ghana.

Methods: Pregnant women (≤20 wk of gestation) were randomized to receive daily: 1) iron and folic acid (IFA) during pregnancy only; 2) multiple micronutrients (MMN; 800 µg retinol equivalent (RE)/capsule), or 3) SQ-LNS (800 µg RE/20g) during pregnancy and the first 6 mo postpartum. Children of mothers in the SQ-LNS group received SQ-LNS (400 µg RE/20 g) from 6 to 18 mo of age; children of mothers in the IFA and MMN groups received no supplement. Plasma retinol was measured in mothers at ≤20 and 36 wk of gestation and 6 mo postpartum, and in children at 6 and 18 mo of age. Milk retinol was measured at 6 mo postpartum. VA status indicators were compared by group.

Results: Among Malawian mothers, geometric mean (95% CI) plasma retinol concentrations at 36 wk of gestation and 6 mo postpartum were 0.97 µmol/L (0.94, 1.01 µmol/L) and 1.35 µmol/L (1.31, 1.39 µmol/L), respectively; geometric mean (95% CI) milk retinol concentration at 6 mo postpartum was 1.04 µmol/L (0.97, 1.13 µmol/L); results did not differ by intervention group. Geometric mean (95% CI) plasma retinol concentrations for Malawian children at 6 and 18 mo of age were 0.78 µmol/L (0.75, 0.81 µmol/L) and 0.81 µmol/L (0.78, 0.85 µmol/L), respectively, and for Ghanaian children they were 0.85 µmol/L (0.82, 0.88 µmol/L) and 0.88 µmol/L (0.85, 0.91 µmol/L), respectively; results did not differ by intervention group in either setting.

Conclusions: SQ-LNS had no effect on VA status of mothers or children, possibly because of low responsiveness of the VA status indicators.

J Nutr. 2020 Nov 19;150(11):3005-3012.
doi: 10.1093/jn/nxaa260.

High-Dose Neonatal Vitamin A Supplementation to Bangladeshi Infants Increases the Percentage of CCR9-Positive Treg Cells in Infants with Lower Birthweight in Early

Infancy, and Decreases Plasma sCD14 Concentration and the Prevalence of Vitamin A Deficiency at Two Years of Age

Shaikh M Ahmad[1], M Nazmul Huda[1 2 3], Rubhana Raqib[1], Firdausi Qadri[1], Md Jahangir Alam[1], Md Nure Alam Afsar[1], Janet M Peerson[2], Sherry A Tanumihardjo[4], Charles B Stephensen[2 3]

Abstract

Background: Vitamin A (VA) stores are low in early infancy and may impair development of the immune system.

Objective: This study determined if neonatal VA supplementation (VAS) affects the following: 1) development of regulatory T (Treg) cells; 2) chemokine receptor 9 (CCR9) expression, which directs mucosal targeting of immune cells; and 3) systemic endotoxin exposure as indicated by changed plasma concentrations of soluble CD14 (sCD14). Secondarily, VA status, growth, and systemic inflammation were investigated.

Methods: In total, 306 Bangladeshi infants were randomly assigned to receive 50,000 IU VA or placebo (PL) within 48 h of birth, and immune function was assessed at 6 wk, 15 wk, and 2 y. Primary outcomes included the following: 1) peripheral blood Treg cells; 2) percentage of Treg, T, and B cells expressing CCR9; and 3) plasma sCD14. Secondary outcomes included the following: 4) VA status measured using the modified relative dose-response (MRDR) test and plasma retinol; 5) infant growth; and 6) plasma C-reactive protein (CRP). Statistical analysis identified group differences and interactions with sex and birthweight.

Results: VAS increased (P = 0.004) the percentage of CCR9+ Treg cells (13.2 ± 1.37%) relative to PL (9.17 ± 1.15%) in children below the median birthweight but had the opposite effect (P = 0.04) in those with higher birthweight (VA, 9.13 ± 0.89; PL, 12.1 ± 1.31%) at 6 and 15 wk (values are combined mean ± SE). VAS decreased (P = 0.003) plasma sCD14 (1.56 ± 0.025 mg/L) relative to PL (1.67 ± 0.032 mg/L) and decreased (P = 0.034) the prevalence of VA deficiency (2.3%) relative to PL (9.2%) at 2 y.

Conclusions: Neonatal VAS enhanced mucosal targeting of Treg cells in low-birthweight infants. The decreased systemic exposure to endotoxin and improved VA status at 2 y may have been due to VA-mediated improvements in gut development resulting in improved barrier function and nutrient absorption.

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Daily consumption of pro-vitamin A biofortified (yellow) cassava improves serum retinol concentrations in preschool children in Nigeria: a randomized controlled trial

Ibukun Afolami[1 2], Martin N Mwangi[1 3], Folake Samuel[2], Erick Boy[4], Paul Ilona[5], Elise F Talsma[1], Edith Feskens[1], Alida Melse-Boonstra[1]

Abstract

Background: Vitamin A deficiency is a public health problem in sub-Saharan Africa. Pro-vitamin A biofortified (yellow) cassava has the potential to contribute significantly to improve vitamin A status, especially in populations that are difficult to reach with other strategies.

Objectives: The study aimed at determining the efficacy of biofortified cassava to improve vitamin A status of Nigerian preschool children.

Methods: An open-label randomized controlled trial was conducted in southwestern Nigeria. In total, 176 preschool children (aged 3-5 y) were randomized into 2 parallel arms comprising

an experimental group (n = 88), fed foods prepared from biofortified (yellow) cassava, and a control group (n = 88), fed foods prepared from white cassava, twice a day, 6 d a week for 93 d.
Results: A total of 159 children completed the trial (yellow cassava group, n = 80; white cassava group, n = 79). Children consumed 221 and 74 µg/d retinol activity equivalents from intervention foods in the yellow and white cassava groups, respectively. The treatment effect on serum retinol concentrations at the end of the feeding trial was 0.06 µmol/L (95% CI: 0.004, 0.124 µmol/L), after adjustment for baseline retinol concentrations, inflammation, and asymptomatic malaria status. No significant treatment effects were detected for serum β-carotene (adjusted effect: 3.9%; 95% CI: -0.6%, 8.6%) and gut permeability (adjusted effect: 0.002; 95% CI: -0.089, 0.092), but a significant effect was detected for hemoglobin concentrations (adjusted effect: 3.08 g/L; 95% CI: 0.38, 5.78 g/L).
Conclusions: Daily consumption of β-carotene from biofortified cassava improved serum retinol and hemoglobin concentrations modestly in Nigerian preschool children.

Vitamin D

(See also Neonates – preterm and low birth weight)

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Vitamin D supplementation and improvement of pneumonic children at a tertiary pediatric hospital in Egypt: A randomized controlled trial
John Rene Labib[1], Sally Kamal Ibrahem[1], Mohamed M Ismail[1], Shaimaa A M Abd El Fatah[2], Amal Samir Sedrak[2], Mona Adel Soliman Attia[2], Hadeel Mohammad El-Hanafi[3], Mai Hamed Kamel[3]
Abstract
Background: Despite the well-recognized effect of vitamin D in metabolism and homeostasis, there is now growing interest in its probable association with pneumonia. This study aims to supply vitamin D3 (Cholecalciferol) (100,000 IU) to pneumonic children to minimize the duration of illness and improve their outcome.
Methods: A double-blinded, randomized, placebo-controlled trial was conducted in a Pediatric Cairo University affiliated hospital. An intervention arm (93 children) and a control arm (98 children), who had pneumonia with an insufficient or deficient level of vitamin D and whose parental permission was obtained, were enrolled in the trial. All children were treated with antibiotics according to WHO guidelines. Children were given a single injection of 1 mL of 100,000 IU of vitamin D3 or placebo. Clinical data were recorded every eight hours for all children. Outcomes were assessed 7 days after vitamin D injection.The primary outcome variable was the change in serum level of 25(OH)D, while the secondary outcomes were the medical state of the assigned cases (improvement or death) and duration between enrollment and hospital discharge for improved cases.
Results: In the supplementation group, the percentage of patients who suffered either deficient (38.7%) or insufficient levels (61.3%) of 25 (OH)D at day one had significantly decreased in the seventh day to (11.8%) and (52.7%), respectively. Kaplan--Meier plots highlighted that the median time to recover of the placebo group was significantly longer than that of the supplementation group (Log Rank P value < .001).

Conclusion: VDD was detected in pediatric critical care children. In pneumonic children with high VDD, it is illustrated that Vitamin D supplementation is accompanied by lowered mortality risk and pSOFA scores, reduced time to recover, and improved PaO2/FiO2.

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Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials

David A Jolliffe[1], Carlos A Camargo Jr[2], John D Sluyter[3], Mary Aglipay[4], John F Aloia[5], Davaasambuu Ganmaa[6], Peter Bergman[7], Heike A Bischoff-Ferrari[8], Arturo Borzutzky[9], Camilla T Damsgaard[10], Gal Dubnov-Raz[11], Susanna Esposito[12], Clare Gilham[13], Adit A Ginde[14], Inbal Golan-Tripto[15], Emma C Goodall[16], Cameron C Grant[17], Christopher J Griffiths[18], Anna Maria Hibbs[19], Wim Janssens[20], Anuradha Vaman Khadilkar[21], Ilkka Laaksi[22], Margaret T Lee[23], Mark Loeb[24], Jonathon L Maguire[4], Paweł Majak[25], David T Mauger[26], Semira Manaseki-Holland[27], David R Murdoch[28], Akio Nakashima[29], Rachel E Neale[30], Hai Pham[30], Christine Rake[13], Judy R Rees[31], Jenni Rosendahl[32], Robert Scragg[3], Dheeraj Shah[33], Yoshiki Shimizu[34], Steve Simpson-Yap[35], Geeta Trilok-Kumar[36], Mitsuyoshi Urashima[29], Adrian R Martineau[37]

Abstract

Background: A 2017 meta-analysis of data from 25 randomised controlled trials (RCTs) of vitamin D supplementation for the prevention of acute respiratory infections (ARIs) revealed a protective effect of this intervention. We aimed to examine the link between vitamin D supplementation and prevention of ARIs in an updated meta-analysis.

Methods: For this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and the ClinicalTrials.gov registry for studies listed from database inception to May 1, 2020. Double-blind RCTs of vitamin D_3, vitamin D_2, or 25-hydroxyvitamin D (25[OH]D) supplementation for any duration, with a placebo or low-dose vitamin D control, were eligible if they had been approved by a research ethics committee, and if ARI incidence was collected prospectively and prespecified as an efficacy outcome. Studies reporting results of long-term follow-up of primary RCTs were excluded. Aggregated study-level data, stratified by baseline 25(OH)D concentration and age, were obtained from study authors. Using the proportion of participants in each trial who had one or more ARIs, we did a random-effects meta-analysis to obtain pooled odds ratios (ORs) and 95% CIs to estimate the effect of vitamin D supplementation on the risk of having one or more ARIs (primary outcome) compared with placebo. Subgroup analyses were done to estimate whether the effects of vitamin D supplementation on the risk of ARI varied according to baseline 25(OH)D concentration (<25 nmol/L vs 25·0-49·9 nmol/L vs 50·0-74·9 nmol/L vs >75·0 nmol/L), vitamin D dose (daily equivalent of <400 international units [IU] vs 400-1000 IU vs 1001-2000 IU vs >2000 IU), dosing frequency (daily vs weekly vs once per month to once every 3 months), trial duration (≤12 months vs >12 months), age at enrolment (<1·00 years vs 1·00-15·99 years vs 16·00-64·99 years vs ≥65·00 years), and presence versus absence of airway disease (ie, asthma only, COPD only, or unrestricted). Risk of bias was assessed with the Cochrane Collaboration Risk of Bias Tool. The study was registered with PROSPERO, CRD42020190633.

Findings: We identified 1528 articles, of which 46 RCTs (75 541 participants) were eligible. Data for the primary outcome were obtained for 48 488 (98·1%) of 49 419 participants (aged

0-95 years) in 43 studies. A significantly lower proportion of participants in the vitamin D supplementation group had one or more ARIs (14 332 [61·3%] of 23 364 participants) than in the placebo group (14 217 [62·3%] of 22 802 participants), with an OR of 0·92 (95% CI 0·86-0·99; 37 studies; I^2=35·6%, $p_{heterogeneity}$=0·018). No significant effect of vitamin D supplementation on the risk of having one or more ARIs was observed for any of the subgroups defined by baseline 25(OH)D concentration. However, protective effects of supplementation were observed in trials in which vitamin D was given in a daily dosing regimen (OR 0·78 [95% CI 0·65-0·94]; 19 studies; I^2=53·5%, $p_{heterogeneity}$=0·003), at daily dose equivalents of 400-1000 IU (0·70 [0·55-0·89]; ten studies; I^2=31·2%, $p_{heterogeneity}$=0·16), for a duration of 12 months or less (0·82 [0·72-0·93]; 29 studies; I^2=38·1%, $p_{heterogeneity}$=0·021), and to participants aged 1·00-15·99 years at enrolment (0·71 [0·57-0·90]; 15 studies; I^2=46·0%, $p_{heterogeneity}$=0·027). No significant interaction between allocation to the vitamin D supplementation group versus the placebo group and dose, dose frequency, study duration, or age was observed. In addition, no significant difference in the proportion of participants who had at least one serious adverse event in the vitamin supplementation group compared with the placebo group was observed (0·97 [0·86-1·07]; 36 studies; I^2=0·0%, $p_{heterogeneity}$=0·99). Risk of bias within individual studies was assessed as being low for all but three trials.
Interpretation: Despite evidence of significant heterogeneity across trials, vitamin D supplementation was safe and overall reduced the risk of ARI compared with placebo, although the risk reduction was small. Protection was associated with administration of daily doses of 400-1000 IU for up to 12 months, and age at enrolment of 1·00-15·99 years. The relevance of these findings to COVID-19 is not known and requires further investigation.

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Vitamin D supplementation in obese Sri Lankan children: a randomized controlled trial

D B D L Samaranayake[1], S G S Adikaram[2], N Atapattu[3], K M D L D Kendaragama[3], J T N Senevirathne[4], H D Jayasekera[4], V P Wickramasinghe[5]

Abstract

Background: Micronutrient deficiencies are identified among obese individuals. Vitamin D deficiency (VDD) is prevalent in obese children, and is hypothesized to cause insulin resistance and metabolic abnormalities. This study aimed to determine the effect of vitamin D supplementation on obesity and related metabolic abnormalities among obese Sri Lankan children with VDD.
Methods: A triple-blind randomized controlled trial was conducted among vitamin D deficient (< 20 ng/ml), obese children (n = 96), randomly allocated to three intervention arms - treatment arm receiving weekly vitamin D_2 50,000 IU; supplementation arm receiving 2500 IU weekly and control arm, receiving placebo. Anthropometry, percentage fat mass (%FM) and blood pressure were assessed and fasting blood glucose, fasting insulin, lipid profile, aspartate transaminase (ALT), alanine transaminase (AST), vitamin D, parathyroid hormone (PTH) and hs-CRP and OGTT with 2-h random blood glucose and insulin was performed at baseline and after 24 weeks of treatment. Ethics Review Committee of Faculty of Medicine, University of Colombo approved the protocol.
Results: Waist circumference Z-score, %FM and serum calcium significantly improved across all three arms, ALT significantly improved in treatment and supplementation arms while, BMI

Z-score, PTH and vitamin D significantly improved in the treatment arm. Biceps (p = 0.035) and subscapular (0.048) skin fold thickness, vitamin D (p = 0.004) and ALT (p = 0.012) significantly improved in the treatment arm.
Conclusions: A strict dietary and physical activity regimen could improve some of the anthropometric, body composition and metabolic profiles, but high dose vitamin D, enhances those improvements. Therefore high dose vitamin D seems to potentiate management outcomes of obese children with vitamin D deficiency.

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Efficacy of vitamin D supplementation in asthmatic children with vitamin D deficiency: A randomized controlled trial (ESDAC trial)

Kana Ram Jat[1], Nancy Goel[1], Nandita Gupta[2], Chandra Prakash Gupta[1], Sudip Datta[3], Rakesh Lodha[1], Sushil K Kabra[1]

Abstract

Background: Vitamin D supplementations for asthma control had shown inconsistent results. We aimed to study efficacy and safety of vitamin D supplementation in asthmatic children who were vitamin D deficient.
Methods: This double-blind, randomized controlled trial enrolled asthmatic children of 4-12 years of age who had 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL. The participants were randomized to receive either vitamin D orally 1000 IU/d for 9 months or similar-looking placebo. The primary outcomes were the proportion of children having the Childhood Asthma Control Test (CACT) score of ≥20 at the end of the treatment and adverse effects.
Results: The trial included 250 children (125 in each group) with a mean age of 8.1 ± 2.3 years and 180 boys. The baseline parameters were similar between the groups, including CACT score (21.7 ± 4.2 vs 21.9 ± 3.6, vitamin D vs placebo). At the end of the study, the proportion of asthmatic children who had CACT score ≥ 20 was similar between vitamin D and placebo group (93.6% vs 92.0%, P = .625). The number of exacerbations of asthma and side effect profile was also identical between the groups. 25(OH)D levels increased significantly in the vitamin D group (18.06 ± 7.11 vs 12.03 ± 5.98 ng/mL, P < .001). The results did not change when we did subgroup analysis for children with baseline CACT score < 20 and 25(OH)D levels at the end of the study ≥20 ng/mL.
Conclusion: Vitamin D supplementation in asthmatic children with vitamin D deficiency did not improve control of asthma.

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Vitamin D for Growth and Rickets in Stunted Children: A Randomized Trial

Francesca L Crowe[1 2], M Zulf Mughal[3 2], Zabihullah Maroof[4 5], Jacqueline Berry[6], Musa Kaleem[7], Sravya Abburu[8], Gijs Walraven[9], Mohammad I Masher[10], Daniel Chandramohan[4], Semira Manaseki-Holland[11 5]

Abstract

Background and objectives: Vitamin D is essential for healthy development of bones, but little is known about the effects of supplementation in young stunted children. Our objective was to assess the effect of vitamin D supplementation on risk of rickets and linear growth among Afghan children.
Methods: In this double-blind, placebo-controlled trial, 3046 children ages 1 to 11 months from inner-city Kabul were randomly assigned to receive oral vitamin D_3 (100 000 IU) or placebo every 3 months for 18 months. Rickets Severity Score was calculated by using wrist and knee radiographs for 631 randomly selected infants at 18 months, and rickets was defined as a score >1.5. Weight and length were measured at baseline and 18 months by using standard techniques, and *z* scores were calculated.
Results: Mean (95% confidence interval [CI]) serum 25-hydroxyvitamin D (seasonally corrected) and dietary calcium intake were insufficient at 37 (35-39) nmol/L and 372 (327-418) mg/day, respectively. Prevalence of rickets was 5.5% (placebo) and 5.3% (vitamin D): odds ratio 0.96 (95% CI: 0.48 to 1.92); *P* = .9. The mean difference in height-for-age *z* score was 0.05 (95% CI: -0.05 to 0.15), *P* = .3, although the effect of vitamin D was greater for those consuming >300 mg/day of dietary calcium (0.14 [95% CI: 0 to 0.29]; *P* = .05). There were no between-group differences in weight-for-age or weight-for-height *z* scores.
Conclusions: Except in those with higher calcium intake, vitamin D supplementation had no effect on rickets or growth.

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Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health

May Loong Tan[1], Steven A Abrams[2], David A Osborn[3]

Abstract
Background: Vitamin D deficiency is common worldwide, contributing to nutritional rickets and osteomalacia which have a major impact on health, growth, and development of infants, children and adolescents. Vitamin D levels are low in breast milk and exclusively breastfed infants are at risk of vitamin D insufficiency or deficiency.
Objectives: To determine the effect of vitamin D supplementation given to infants, or lactating mothers, on vitamin D deficiency, bone density and growth in healthy term breastfed infants.
Search methods: We used the standard search strategy of Cochrane Neonatal to 29 May 2020 supplemented by searches of clinical trials databases, conference proceedings, and citations.
Selection criteria: Randomised controlled trials (RCTs) and quasi-RCTs in breastfeeding mother-infant pairs comparing vitamin D supplementation given to infants or lactating mothers compared to placebo or no intervention, or sunlight, or that compare vitamin D supplementation of infants to supplementation of mothers.
Data collection and analysis: Two review authors assessed trial eligibility and risk of bias and independently extracted data. We used the GRADE approach to assess the certainty of evidence.
Main results: We included 19 studies with 2837 mother-infant pairs assessing vitamin D given to infants (nine studies), to lactating mothers (eight studies), and to infants versus lactating mothers (six studies). No studies compared vitamin D given to infants versus

periods of infant sun exposure. Vitamin D supplementation given to infants: vitamin D at 400 IU/day may increase 25-OH vitamin D levels (MD 22.63 nmol/L, 95% CI 17.05 to 28.21; participants = 334; studies = 6; low-certainty) and may reduce the incidence of vitamin D insufficiency (25-OH vitamin D < 50 nmol/L) (RR 0.57, 95% CI 0.41 to 0.80; participants = 274; studies = 4; low-certainty). However, there was insufficient evidence to determine if vitamin D given to the infant reduces the risk of vitamin D deficiency (25-OH vitamin D < 30 nmol/L) up till six months of age (RR 0.41, 95% CI 0.16 to 1.05; participants = 122; studies = 2), affects bone mineral content (BMC), or the incidence of biochemical or radiological rickets (all very-low certainty). We are uncertain about adverse effects including hypercalcaemia. There were no studies of higher doses of infant vitamin D (> 400 IU/day) compared to placebo. Vitamin D supplementation given to lactating mothers: vitamin D supplementation given to lactating mothers may increase infant 25-OH vitamin D levels (MD 24.60 nmol/L, 95% CI 21.59 to 27.60; participants = 597; studies = 7; low-certainty), may reduce the incidences of vitamin D insufficiency (RR 0.47, 95% CI 0.39 to 0.57; participants = 512; studies = 5; low-certainty), vitamin D deficiency (RR 0.15, 95% CI 0.09 to 0.24; participants = 512; studies = 5; low-certainty) and biochemical rickets (RR 0.06, 95% CI 0.01 to 0.44; participants = 229; studies = 2; low-certainty). The two studies that reported biochemical rickets used maternal dosages of oral D3 60,000 IU/day for 10 days and oral D3 60,000 IU postpartum and at 6, 10, and 14 weeks. However, infant BMC was not reported and there was insufficient evidence to determine if maternal supplementation has an effect on radiological rickets (RR 0.76, 95% CI 0.18 to 3.31; participants = 536; studies = 3; very low-certainty). All studies of maternal supplementation enrolled populations at high risk of vitamin D deficiency. We are uncertain of the effects of maternal supplementation on infant growth and adverse effects including hypercalcaemia. Vitamin D supplementation given to infants compared with supplementation given to lactating mothers: infant vitamin D supplementation compared to lactating mother supplementation may increase infant 25-OH vitamin D levels (MD 14.35 nmol/L, 95% CI 9.64 to 19.06; participants = 269; studies = 4; low-certainty). Infant vitamin D supplementation may reduce the incidence of vitamin D insufficiency (RR 0.61, 95% CI 0.40 to 0.94; participants = 334; studies = 4) and may reduce vitamin D deficiency (RR 0.35, 95% CI 0.17 to 0.72; participants = 334; studies = 4) but the evidence is very uncertain. Infant BMC and radiological rickets were not reported and there was insufficient evidence to determine if maternal supplementation has an effect on infant biochemical rickets. All studies enrolled patient populations at high risk of vitamin D deficiency. Studies compared an infant dose of vitamin D 400 IU/day with varying maternal vitamin D doses from 400 IU/day to > 4000 IU/day. We are uncertain about adverse effects including hypercalcaemia.

Authors' conclusions: For breastfed infants, vitamin D supplementation 400 IU/day for up to six months increases 25-OH vitamin D levels and reduces vitamin D insufficiency, but there was insufficient evidence to assess its effect on vitamin D deficiency and bone health. For higher-risk infants who are breastfeeding, maternal vitamin D supplementation reduces vitamin D insufficiency and vitamin D deficiency, but there was insufficient evidence to determine an effect on bone health. In populations at higher risk of vitamin D deficiency, vitamin D supplementation of infants led to greater increases in infant 25-OH vitamin D levels, reductions in vitamin D insufficiency and vitamin D deficiency compared to supplementation of lactating mothers. However, the evidence is very uncertain for markers of bone health. Maternal higher dose supplementation (≥ 4000 IU/day) produced similar infant 25-OH vitamin D levels as infant supplementation of 400 IU/day. The certainty of evidence was graded as low to very low for all outcomes.

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Effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age

Samantha L Huey[1], Nina Acharya[1], Ashley Silver[1], Risha Sheni[1], Elaine A Yu[1], Juan Pablo Peña-Rosas[2], Saurabh Mehta[1]

Abstract

Background: Vitamin D is a secosteroid hormone that is important for its role in calcium homeostasis to maintain skeletal health. Linear growth faltering and stunting remain pervasive indicators of poor nutrition status among infants and children under five years of age around the world, and low vitamin D status has been linked to poor growth. However, existing evidence on the effects of vitamin D supplementation on linear growth and other health outcomes among infants and children under five years of age has not been systematically reviewed.

Objectives: To assess effects of oral vitamin D supplementation on linear growth and other health outcomes among infants and children under five years of age.

Search methods: In December 2019, we searched CENTRAL, PubMed, Embase, 14 other electronic databases, and two trials registries. We also searched the reference lists of relevant publications for any relevant trials, and we contacted key organisations and authors to obtain information on relevant ongoing and unpublished trials.

Selection criteria: We included randomised controlled trials (RCTs) and quasi-RCTs assessing the effects of oral vitamin D supplementation, with or without other micronutrients, compared to no intervention, placebo, a lower dose of vitamin D, or the same micronutrients alone (and not vitamin D) in infants and children under five years of age who lived in any country.

Data collection and analysis: We used standard Cochrane methodological procedures.

Main results: Out of 75 studies (187 reports; 12,122 participants) included in the qualitative analysis, 64 studies (169 reports; 10,854 participants) contributed data on our outcomes of interest for meta-analysis. A majority of included studies were conducted in India, USA, and Canada. Two studies reported for-profit funding, two were categorised as receiving mixed funding (non-profit and for-profit), five reported that they received no funding, 26 did not disclose funding sources, and the remaining studies were funded by non-profit funding. Certainty of evidence varied between high and very low across outcomes (all measured at endpoint) for each comparison. Vitamin D supplementation versus placebo or no intervention (31 studies) Compared to placebo or no intervention, vitamin D supplementation (at doses 200 to 2000 IU daily; or up to 300,000 IU bolus at enrolment) may make little to no difference in linear growth (measured length/height in cm) among children under five years of age (mean difference (MD) 0.66, 95% confidence interval (CI) -0.37 to 1.68; 3 studies, 240 participants; low-certainty evidence); probably improves length/height-for-age z-score (L/HAZ) (MD 0.11, 95% CI 0.001 to 0.22; 1 study, 1258 participants; moderate-certainty evidence); and probably makes little to no difference in stunting (risk ratio (RR) 0.90, 95% CI 0.80 to 1.01; 1 study, 1247 participants; moderate-certainty evidence). In terms of adverse events, vitamin D supplementation results in little to no difference in developing hypercalciuria compared to placebo (RR 2.03, 95% CI 0.28 to 14.67; 2 studies, 68 participants;

high-certainty evidence). It is uncertain whether vitamin D supplementation impacts the development of hypercalcaemia as the certainty of evidence was very low (RR 0.82, 95% CI 0.35 to 1.90; 2 studies, 367 participants). Vitamin D supplementation (higher dose) versus vitamin D (lower dose) (34 studies) Compared to a lower dose of vitamin D (100 to 1000 IU daily; or up to 300,000 IU bolus at enrolment), higher-dose vitamin D supplementation (200 to 6000 IU daily; or up to 600,000 IU bolus at enrolment) may have little to no effect on linear growth, but we are uncertain about this result (MD 1.00, 95% CI -2.22 to 0.21; 5 studies, 283 participants), and it may make little to no difference in L/HAZ (MD 0.40, 95% CI -0.06 to 0.86; 2 studies, 105 participants; low-certainty evidence). No studies evaluated stunting. As regards adverse events, higher-dose vitamin D supplementation may make little to no difference in developing hypercalciuria (RR 1.16, 95% CI 1.00 to 1.35; 6 studies, 554 participants; low-certainty evidence) or in hypercalcaemia (RR 1.39, 95% CI 0.89 to 2.18; 5 studies, 986 participants; low-certainty evidence) compared to lower-dose vitamin D supplementation. Vitamin D supplementation (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s) (9 studies) Supplementation with a higher dose of vitamin D (400 to 2000 IU daily, or up to 300,000 IU bolus at enrolment) plus micronutrients, compared to a lower dose (200 to 2000 IU daily, or up to 90,000 IU bolus at enrolment) of vitamin D with the same micronutrients, probably makes little to no difference in linear growth (MD 0.60, 95% CI -3.33 to 4.53; 1 study, 25 participants; moderate-certainty evidence). No studies evaluated L/HAZ or stunting. In terms of adverse events, higher-dose vitamin D supplementation with micronutrients, compared to lower-dose vitamin D with the same micronutrients, may make little to no difference in developing hypercalciuria (RR 1.00, 95% CI 0.06 to 15.48; 1 study, 86 participants; low-certainty evidence) and probably makes little to no difference in developing hypercalcaemia (RR 1.00, 95% CI 0.90, 1.11; 2 studies, 126 participants; moderate-certainty evidence). Four studies measured hyperphosphataemia and three studies measured kidney stones, but they reported no occurrences and therefore were not included in the comparison for these outcomes.

Authors' conclusions: Evidence suggests that oral vitamin D supplementation may result in little to no difference in linear growth, stunting, hypercalciuria, or hypercalcaemia, compared to placebo or no intervention, but may result in a slight increase in length/height-for-age z-score (L/HAZ). Additionally, evidence suggests that compared to lower doses of vitamin D, with or without micronutrients, vitamin D supplementation may result in little to no difference in linear growth, L/HAZ, stunting, hypercalciuria, or hypercalcaemia. Small sample sizes, substantial heterogeneity in terms of population and intervention parameters, and high risk of bias across many of the included studies limit our ability to confirm with any certainty the effects of vitamin D on our outcomes. Larger, well-designed studies of long duration (several months to years) are recommended to confirm whether or not oral vitamin D supplementation may impact linear growth in children under five years of age, among both those who are healthy and those with underlying infectious or non-communicable health conditions.

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Vitamin D Treatment during Pregnancy and Maternal and Neonatal Cord Blood Metal Concentrations at Delivery: Results of a Randomized Controlled Trial in Bangladesh

Anne Marie Z Jukic[1], Anna Zuchniak[2 3], Huma Qamar[3], Tahmeed Ahmed[4], Abdullah Al Mahmud[4], Daniel E Roth[2 3 5]

Abstract

Background: Vitamin D improves absorption of calcium; however, in animal studies vitamin D also increases the absorption of toxic metals, such as lead and cadmium.

Objectives: We examined maternal and neonatal cord blood levels of lead, cadmium, manganese, and mercury after supplementation with vitamin D during pregnancy.

Methods: The Maternal Vitamin D for Infant Growth trial was a randomized, placebo-controlled, multi-arm study of maternal vitamin D supplementation during pregnancy in Dhaka, Bangladesh (NCT01924013). Women were randomized during their second trimester to blinded weekly doses of placebo or 4,200, 16,800, or 28,000 IU of vitamin D3 throughout pregnancy. Each group had 118-239 maternal blood specimens and 100-201 cord blood samples analyzed. Metals were measured using inductively coupled plasma mass spectrometry. Unadjusted estimates from linear regression models were expressed as percentage differences. Cord blood cadmium was analyzed as detectable or undetectable with log-binomial regression.

Results: Maternal cadmium, mercury, and manganese levels were nearly identical across groups. Maternal lead levels were 6.3%, 7.4%, and 6.0% higher in the treatment groups (4,200, 16,800, and 28,000 IU, respectively) vs. placebo; however, 95% confidence intervals (CIs) showed that differences from 4.1% lower to 20% higher were compatible with the data. In treatment groups (4,200, 16,800, 28,000 IU) vs. placebo, neonatal cord blood lead levels were 8.5% (95% CI: −3.5-3.5, 22), 16% (95% CI: 3.3, 30), and 11% (95% CI: 0.4, 23) higher and had higher risk of detectable cadmium, relative risk (RR)=2.2(RR)=2.2 (95% CI: 1.3, 3.7), RR=1.4RR=1.4 (95% CI: 0.8, 2.5), RR=1.7RR=1.7 (95% CI: 1.0, 2.9).

Discussion: Vitamin D supplementation from the second trimester of pregnancy did not influence maternal cadmium, mercury, or manganese levels at delivery. Vitamin D was associated with nonsignificant increases in maternal lead and with significant increases in cord blood lead and cadmium. These associations were not dose dependent. Given that there are no safe levels of metals in infants, the observed increases in cord blood lead and cadmium require further exploration.

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The Health Effects of Vitamin D and Probiotic Co-Supplementation: A Systematic Review of Randomized Controlled Trials

Myriam Abboud[1], Rana Rizk[2], Fatme AlAnouti[1], Dimitrios Papandreou[1], Suzan Haidar[3], Nadine Mahboub[3 4]

Abstract

Evidence of synergic health effects of co-supplementation with vitamin D and probiotics is emerging. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA statement, scientific databases and the grey literature were searched, and a narrative review and risk of bias assessment were conducted. Seven randomized controlled trials were included, which had low risk of bias. Six studies were double-blind, and once single-blind, extended over 6-12 weeks, and included 50-105 participants. Conditions explored included schizophrenia, gestational diabetes, type 2 diabetes and coronary heart

disease, polycystic ovarian syndrome, osteopenia, irritable bowel syndrome (IBS), and infantile colic. Supplementation frequency was daily or bi-monthly, with mainly vitamin D3, and *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. Comparators were placebo, vitamin D, lower vitamin D dose, and probiotics and lower vitamin D dose. The co-supplementation yielded greater health benefits than its comparators did in all studies except in one assessing IBS. Beneficial effects included decreased disease severity, improved mental health, metabolic parameters, mainly insulin sensitivity, dyslipidemia, inflammation, and antioxidative capacity, and lower use of healthcare. Co-supplementation of vitamin D and probiotics generated greater health benefits than its comparators did. More studies in other diseases and various populations are needed to confirm these findings and to elucidate the optimal form, composition, and frequency of this co-supplementation.

Yaws

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Antibody Responses to Two Recombinant Treponemal Antigens (rp17 and TmpA) before and after Azithromycin Treatment for Yaws in Ghana and Papua New Guinea

Nishanth Parameswaran[1], Oriol Mitjà[2 3], Christian Bottomley[4], Cynthia Kwakye[5], Wendy Houinei[6], Allan Pillay[7], Damien Danavall[7], Kai-Hua Chi[7], Ronald C Ballard[8], Anthony W Solomon[9], Cheng Y Chen[7], Sibauk V Bieb[10], Yaw Adu-Sarkodie[5], David C W Mabey[11 12], Kingsley Asiedu[9], Michael Marks[11 12], Diana L Martin[13]

Abstract

WHO and its partners aim to interrupt yaws transmission in countries of endemicity and to certify others as being yaws-free. Transmission can be assessed using rapid plasma reagin (RPR) tests, reflecting current or recent infection, but RPR is operationally impractical. We evaluated changes in antibody levels against two recombinant treponemal antigens, rp17 (also known as Tp17) and TmpA, after antibiotic treatment given as part of a randomized controlled trial for yaws in Ghana and Papua New Guinea. Paired serum samples from children aged 6 to 15 years with confirmed yaws, collected before and after treatment, were tested for antibodies to rp17 and TmpA using a semiquantitative bead-based immunoassay. Of 344 baseline samples, 342 tested positive for anti-rp17 antibodies and 337 tested positive for anti-TmpA antibodies. Six months after treatment, the median decrease in anti-rp17 signal was 3.2%, whereas the median decrease in anti-TmpA was 53.8%. The magnitude of change in the anti-TmpA response increased with increasing RPR titer fold change. These data demonstrate that responses to TmpA decrease markedly within 6 months of treatment whereas (as expected) those to rp17 do not. Incorporating responses to TmpA as a marker of recent infection within an integrated sero-surveillance platform could provide a way to prioritize areas for yaws mapping.

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

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Lower-Dose Zinc for Childhood Diarrhea - A Randomized, Multicenter Trial

Usha Dhingra[1], Rodrick Kisenge[1], Christopher R Sudfeld[1], Pratibha Dhingra[1], Sarah Somji[1], Arup Dutta[1], Mohamed Bakari[1], Saikat Deb[1], Prabhabati Devi[1], Enju Liu[1], Aishwarya Chauhan[1], Jitendra Kumar[1], Om P Semwal[1], Said Aboud[1], Rajiv Bahl[1], Per Ashorn[1], Jonathon Simon[1], Christopher P Duggan[1], Sunil Sazawal[1], Karim Manji[1]

Abstract

Background: The World Health Organization recommends 20 mg of zinc per day for 10 to 14 days for children with acute diarrhea; in previous trials, this dosage decreased diarrhea but increased vomiting.

Methods: We randomly assigned 4500 children in India and Tanzania who were 6 to 59 months of age and had acute diarrhea to receive 5 mg, 10 mg, or 20 mg of zinc sulfate for 14 days. The three primary outcomes were a diarrhea duration of more than 5 days and the number of stools (assessed in a noninferiority analysis) and the occurrence of vomiting (assessed in a superiority analysis) within 30 minutes after zinc administration.

Results: The percentage of children with diarrhea for more than 5 days was 6.5% in the 20-mg group, 7.7% in the 10-mg group, and 7.2% in the 5-mg group. The difference between the 20-mg and 10-mg groups was 1.2 percentage points (upper boundary of the 98.75% confidence interval [CI], 3.3), and that between the 20-mg and 5-mg groups was 0.7 percentage points (upper boundary of the 98.75% CI, 2.8), both of which were below the noninferiority margin of 4 percentage points. The mean number of diarrheal stools was 10.7 in the 20-mg group, 10.9 in the 10-mg group, and 10.8 in 5-mg group. The difference between the 20-mg and 10-mg groups was 0.3 stools (upper boundary of the 98.75% CI, 1.0), and that between the 20-mg and 5-mg groups was 0.1 stools (upper boundary of the 98.75% CI, 0.8), both of which were below the noninferiority margin (2 stools). Vomiting within 30 minutes after administration occurred in 19.3%, 15.6%, and 13.7% of the patients in the 20-mg, 10-mg, and 5-mg groups, respectively; the risk was significantly lower in the 10-mg group than in the 20-mg group (relative risk, 0.81; 97.5% CI, 0.67 to 0.96) and in the 5-mg group than in the 20-mg group (relative risk, 0.71; 97.5% CI, 0.59 to 0.86). Lower doses were also associated with less vomiting beyond 30 minutes after administration.

Conclusions: Lower doses of zinc had noninferior efficacy for the treatment of diarrhea in children and were associated with less vomiting than the standard 20-mg dose

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Daily Preventive Zinc Supplementation Decreases Lymphocyte and Eosinophil Concentrations in Rural Laotian Children from Communities with a High Prevalence of Zinc Deficiency: Results of a Randomized Controlled Trial

Chidchamai Kewcharoenwong[1], Gertrud U Schuster[2,3], K Ryan Wessells[2], Guy-Marino Hinnouho[2], Maxwell A Barffour[2,4], Sengchanh Kounnavong[5], Kenneth H Brown[2], Sonja Y Hess[2], Waraporn Samer[1], Inthira Tussakhon[1,6], Janet M Peerson[3], Ganjana Lertmemongkolchai[1], Charles B Stephensen[2,3]

Abstract

Background: Zinc deficiency impairs immune function and is common among children in South-East Asia.
Objectives: The effect of zinc supplementation on immune function in young Laotian children was investigated.
Methods: Children (n = 512) aged 6-23 mo received daily preventive zinc tablets (PZ; 7 mg Zn/d), daily multiple micronutrient powder (MNP; 10 mg Zn/d, 6 mg Fe/d, plus 13 other micronutrients), therapeutic dispersible zinc tablets only in association with diarrhea episodes (TZ; 20 mg Zn/d for 10 d after an episode), or daily placebo powder (control). These interventions continued for 9 mo. Cytokine production from whole blood cultures, the concentrations of T-cell populations, and a complete blood count with differential leukocyte count were measured at baseline and endline. Endline means were compared via ANCOVA, controlling for the baseline value of the outcome, child age and sex, district, month of enrollment, and baseline zinc status (below, or above or equal to, the median plasma zinc concentration).
Results: T-cell cytokines (IL-2, IFN-γ, IL-13, IL-17), LPS-stimulated cytokines (IL-1β, IL-6, TNF-α, and IL-10), and T-cell concentrations at endline did not differ between intervention groups, nor was there an interaction with baseline zinc status. However, mean ± SE endline lymphocyte concentrations were significantly lower in the PZ than in the control group (5018 ± 158 compared with 5640 ± 160 cells/μL, P = 0.032). Interactions with baseline zinc status were seen for eosinophils (Pixn = 0.0036), basophils (Pixn = 0.023), and monocytes (P = 0.086) but a significant subgroup difference was seen only for eosinophils, where concentrations were significantly lower in the PZ than in the control group among children with baseline plasma zinc concentrations below the overall median (524 ± 44 compared with 600 ± 41 cells/μL, P = 0.012).
Conclusions: Zinc supplementation of rural Laotian children had no effect on cytokines or T-cell concentrations, although zinc supplementation affected lymphocyte and eosinophil concentrations. These cell subsets may be useful as indicators of response to zinc supplementation.This trial was registered at clinicaltrials.gov as NCT02428647.

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Enteral zinc supplementation for prevention of morbidity and mortality in preterm neonates

Eveline Staub[1], Katrina Evers[2], Lisa M Askie[3]

Abstract
Background: Preterm and low birth weight infants are born with low stores in zinc, which is a vital trace element for growth, cell differentiation and immune function. Preterm infants are at risk of zinc deficiency during the postnatal period of rapid growth. Systematic reviews in the older paediatric population have previously shown that zinc supplementation potentially improves growth and positively influences the course of infectious diseases. In paediatric reviews, the effect of zinc supplementation was most pronounced in those with low nutritional status, which is why the intervention could also benefit preterm infants typically born with low zinc stores and decreased immunity.

Objectives: To determine whether enteral zinc supplementation, compared with placebo or no supplementation, affects important outcomes in preterm infants, including death, neurodevelopment, common morbidities and growth.
Search methods: Our searches are up-to-date to 20 February 2020. For the first search, we used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 8), MEDLINE via PubMed (1966 to 29 September 2017), Embase (1980 to 29 September 2017), and CINAHL (1982 to 29 September 2017). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-RCTs. We ran an updated search from 1 January 2017 to 20 February 2020 in the following databases: CENTRAL via CRS Web, MEDLINE via Ovid, and CINAHL via EBSCOhost.
Selection criteria: We included RCTs and quasi-RCTs that compared enteral zinc supplementation versus placebo or no supplementation in preterm infants (gestational age < 37 weeks), and low birth weight babies (birth weight < 2500 grams), at any time during their hospital admission after birth. We included zinc supplementation in any formulation, regimen, or dose administered via the enteral route. We excluded infants who underwent gastrointestinal (GI) surgery during their initial hospital stay, or had a GI malformation or another condition accompanied by abnormal losses of GI juices, which contain high levels of zinc (including, but not limited to, stomas, fistulas, and malabsorptive diarrhoea).
Data collection and analysis: We used the standard methods of Cochrane Neonatal. Two review authors separately screened abstracts, evaluated trial quality and extracted data. We synthesised effect estimates using risk ratios (RR), risk differences (RD), and standardised mean differences (SMD). Our primary outcomes of interest were all-cause mortality and neurodevelopmental disability. We used the GRADE approach to assess the certainty of evidence.
Main results: We included five trials with a total of 482 preterm infants; there was one ongoing trial. The five included trials were generally small, but of good methodological quality. Enteral zinc supplementation compared to no zinc supplementation Enteral zinc supplementation started in hospitalised preterm infants may decrease all-cause mortality (between start of intervention and end of follow-up period) (RR 0.55, 95% CI 0.31 to 0.97; 3 studies, 345 infants; low-certainty evidence). No data were available on long-term neurodevelopmental outcomes at 18 to 24 months of (post-term) age. Enteral zinc supplementation may have little or no effect on common morbidities such as bronchopulmonary dysplasia (RR 0.66, 95% CI 0.31 to 1.40, 1 study, 193 infants; low-certainty evidence), retinopathy of prematurity (RR 0.14, 95% CI 0.01 to 2.70, 1 study, 193 infants; low-certainty evidence), bacterial sepsis (RR 1.11, 95% CI 0.60 to 2.04, 2 studies, 293 infants; moderate-certainty evidence), or necrotising enterocolitis (RR 0.08, 95% CI 0.00 to 1.33, 1 study, 193 infants; low-certainty evidence). The intervention probably improves weight gain (SMD 0.46, 95% CI 0.28 to 0.64; 5 studies, 481 infants; moderate-certainty evidence); and may slightly improve linear growth (SMD 0.75, 95% CI 0.36 to 1.14, 3 studies, 289 infants; low-certainty evidence), but may have little or no effect on head growth (SMD 0.21, 95% CI -0.02 to 0.44, 3 studies, 289 infants; moderate-certainty evidence).
Authors' conclusions: Enteral supplementation of zinc in preterm infants compared to no supplementation or placebo may moderately decrease mortality and probably improve short-term weight gain and linear growth, but may have little or no effect on common morbidities of prematurity. There are no data to assess the effect of zinc supplementation on long-term neurodevelopment.

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Does zinc with and without iron co-supplementation have effect on motor and mental development of children? A systematic review and meta-analysis

Firoozeh Sajedi[1], Soheila Shahshahani[1], Hesam Ghiasvand[1 2], Zahra Mosallanezhad[3 4], Shiva Fatollahierad[5]

Abstract

Background: Effects of zinc with and without iron co-supplementation on child development are uncertain therefore the aims of this systematic review were to explore whether supplementation with zinc alone and zinc with iron in children aged 0-5 years old have beneficial or adverse effects on their mental and motor development.

Method: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science and Scopus until July 2020 and included randomized controlled trials, which assessed effects of zinc supplementation with and without iron in children less than 5 years old on mental and motor development. Data were pooled by random effects model and the Standardized Mean Differences (SMDs) with 95% confidence interval were estimated. The heterogeneity was assessed by I^2.

Results: Twenty-five studies with 11,559 participants were eligible to be included in this systematic review. Meta-analysis was conducted with eight articles that used Bayley Scales of Infant and Toddler Development II. We concluded that zinc alone and zinc with iron co-supplementation do not have beneficial or adverse effect on child mental and motor development at 6 and 12 months of age with low to moderate quality of the evidence. Furthermore, Zinc supplementation does not have any long term effect on child development in preschool and school age children.

Conclusion: Most included studies did not show the efficacy of zinc with and without iron co-supplementation on child mental and motor development up to 9 years old age. Further Randomized Controlled Trials (RCTs) need to be taken into considerations the context-based differences between countries with special focus on socio-economic differences.

Keywords: Child; Development; Iron; Zinc.

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Zinc supplementation for improving pregnancy and infant outcome

Bianca Carducci[1], Emily C Keats[1], Zulfiqar A Bhutta[1]

Abstract

Background: It has been suggested that low serum zinc levels may be associated with suboptimal outcomes of pregnancy, such as prolonged labour, atonic postpartum haemorrhage, pregnancy-induced hypertension, preterm labour and post-term pregnancies, although these associations have not yet been established. This is an update of a review first published in 1997 and subsequently updated in 2007, 2012 and 2015.

Objectives: 1. To compare the effects on maternal, fetal, neonatal and infant outcomes in healthy pregnant women receiving zinc supplementation versus no zinc supplementation, or placebo. 2. To assess the above outcomes in a subgroup analysis reviewing studies performed in women who are, or are likely to be, zinc-deficient.
Search methods: For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (3 July 2020), and reference lists of retrieved studies.
Selection criteria: Randomised trials of zinc supplementation versus no zinc supplementation or placebo administration during pregnancy, earlier than 27 weeks' gestation. We excluded quasi-randomised controlled trials. We intended to include studies presented only as abstracts, if they provided enough information or, if necessary, by contacting authors to analyse them against our criteria; we did not find any such studies.
Data collection and analysis: Three review authors applied the study selection criteria, assessed trial quality and extracted data. When necessary, we contacted study authors for additional information. We assessed the certainty of the evidence using GRADE.
Main results: For this update, we included 25 randomised controlled trials (RCTs) involving over 18,000 women and their babies. The overall risk of bias was low in half of the studies. The evidence suggests that zinc supplementation may result in little or no difference in reducing preterm births (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.74 to 1.03; 21 studies, 9851 participants; low-certainty evidence). Further, zinc supplementation may make little or no difference in reducing the risk of stillbirth (RR 1.22, 95% CI 0.80 to 1.88; 7 studies, 3295 participants; low-certainty evidence), or perinatal deaths (RR 1.10, 95% CI 0.81 to 1.51; 2 studies, 2489 participants; low-certainty evidence). It is unclear whether zinc supplementation reduces neonatal death, because the certainty of the evidence is very low. Finally, for other birth outcomes, zinc supplementation may make little or no difference to mean birthweight (MD 13.83, 95% CI -15.81 to 43.46; 22 studies, 7977 participants; low-certainty evidence), and probably makes little or no difference in reducing the risk of low birthweight (RR 0.94, 95% CI 0.79 to 1.13; 17 studies, 7399 participants; moderate-certainty evidence) and small-for-gestational age babies when compared to placebo or no zinc supplementation (RR 1.02, 95% CI 0.92 to 1.12; 9 studies, 5330 participants; moderate-certainty evidence). We did not conduct subgroup analyses, as very few studies used normal zinc populations.
Authors' conclusions: There is not enough evidence that zinc supplementation during pregnancy results in improvements in maternal or neonatal outcomes. Future research to address ways of improving the overall nutritional status of pregnant women, particularly in low-income regions, and not looking at zinc in isolation, should be an urgent priority.

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Prevalence of Zinc Deficiency and the Effect of Zinc Supplementation on the Prevention of Acute Respiratory Infections

Daisy Khera[1], Surjit Singh[2], Purvi Purohit[3], Praveen Sharma[3], Kuldeep Singh[1]

Abstract
Objective: Acute lower respiratory infections are an important cause of morbidity and mortality in developing countries. Recent randomized trials of zinc supplementation for the

prevention of acute lower respiratory tract infections have revealed discrepant findings. The main aim of this study was to evaluate the prevalence of zinc deficiency and the effect of zinc supplementation on respiratory infections.
Material and methods: A single center, prospective open-label interventional single-arm pre-post study of the effect of oral zinc supplementation in zinc deficient children aged 6 months to 5 years was done. A total of 465 healthy children of age 6 months to 5 years were enrolled in the study for estimation of the prevalence of zinc deficiency. Children having zinc deficiency were recruited to study the efficacy and safety of oral administration of 20 mg zinc for two weeks during a 6-month follow-up period.
Results: There were statistically significant differences between the zinc deficient and non-deficient groups according to modified Kuppuswamy categorization of family status and exclusive breast feeding. There was significant difference in the mid arm circumference between the zinc deficient and non-deficient groups ($p<0.001$). There was significant difference ($p<0.001$) in the number of episodes of acute upper respiratory infections (AURI), mean duration of AURI, and acute lower respiratory infections (ALRI) between the two groups. There was no significant difference in the ALRI episodes between the two groups. After zinc supplementation in zinc deficient children, there was significant decrease in the number of episodes and mean duration of AURI ($p<0.001$) and ALRI ($p<0.001$) within six months after supplementation as compared with the preceding six months before supplementation.
Conclusion: This study reveals that a short course of zinc supplementation may reduce the burden of AURI/ALRI among the zinc deficient children, but larger studies are needed.