RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

13th Edition
July 2014-June 2015

www.ichrc.org

Please send suggestions about this booklet to:

Prof Trevor Duke
Centre for International Child Health
University of Melbourne, Department of Paediatrics
Royal Children's Hospital
Parkville, 3052, Victoria, Australia
Telephone: (613) 9345 5968
Email: **trevor.duke@rch.org.au**

SEARCH STRATEGY

Pubmed Advanced strategy, search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR Asia-Pacific) and (Child*)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) publication date between July 1st 2014 and June 30th 2015.

Introduction

This booklet is compiled annually to summarize the evidence on child 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. It is hoped that such information will be helpful in reviewing treatment policies, clinical practice and public health strategies.

The method of searching for studies to include uses PubMed, a search engine that is freely available and widely used in most 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 far from 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. However their results should not be accepted uncritically and 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 the wider applicability, feasibility and potential for sustainability.

This year 245 studies were identified. These came from all regions of the world, mostly from developing country researchers. Several trials from 2014-15 will lead to significant changes in child health approaches or clinical recommendations.

We have included the web-link for papers that are available in full-text on the Internet free of charge. 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.

Please feel free to distribute this booklet to any colleagues. The previous editions (2002-2014) are available at: www.ichrc.org

Two years ago we published a summary of the first 11 years of the controlled trials. The reference for this is: Duke T, Fuller D. Arch Dis Child 2014, 99:615–620, and you may download it at: **http://adc.bmj.com/content/99/7/615.full.pdf+html**

A brief summary of some of the important results in 2014-15

- In a high-mortality setting in Kenya where co-morbidities are common, among children with non-severe pneumonia, oral amoxicillin was non-inferior to intravenous benzylpenicillin, and failure rates at day 14 were 13.5 and 16.8% respectively. In Brazil oral amocycillin given 2 times per day was as effective as 3 times per day in treating non-severe pneumonia

with treatment failure rates of 23% and 22% respectively.

- Children in African hospitals with severe anaemia were more likely to die in the first 24 hours (case fatality rate 13%) than those with mild or moderate anaemia (7-8%). Children with severe anaemia who were not transfused at 2.5 hours had a much higher risk of dying than those who received blood early.

- For Indian children with central nervous system infections cared for in an intensive care unit, the targeting of a cerebral perfusion pressure >60mmHg using fluid boluses, and dopamine / noradrenaline, resulted in lower mortality and less neuro-disability than a strategy aiming to keep intracranial pressure <20 mmHg with osmotherapy while ensuring a normal blood pressure.

- In over 1000 Colombian children in the second year of life, a weekly home visiting program where play was taught over 18 months improved cognitive scores and receptive language. Micronutrient supplementation had no effect on developmental outcomes in this trial.

- In rural children in India, Pakistan and Zambia, an early developmental intervention taught to parents over 3 years improved cognitive abilities regardless of the type of development risk the child faced.

- Using a test of "intestinal permeability", the lactulose: mannitol urinary excretion test, for children at risk of environmental enteropathy, zinc or albendazole reduced the apparent progression of intestinal permeability.

- Among 50 Indian children with type-1 diabetes and ketoacidosis, use of insulin infusion at 0.05 U/kg/hour was associated with resolution of acidosis and ketosis, with lower risk of hypoglycaemia than the standard infusion of 0.1 U/kg/hour.

- In African children with prolonged convulsions use of intra-rectal diazepam was more effective in controlling seizures than sublingual lorazepam.

- Among Indian children with infantile spasms, use of high-dose prednisolone (4mg/kg/day) was more effective than 2mg/kg/day in leading to cessation of spasms by 2 weeks.

- In 80 rural villages, India's total sanitation campaign, designed to end the practice of open defecation by provision of individual household latrines, reduced open defecation by 10% and improved sanitation facilities by 19%. These are modest early gains, as yet insufficient to improve child health outcomes, but would be expected to grow over time.

- And this year, an RCT of soap! In Bangladesh, use of soapy water (30g powdered detergent in 1.5 L water) or bar soap, scrubbing hands for 15 seconds were both more effective in reducing coliforms than scrubbing with plain water!

- In adolescents and adults in sub-Saharan Africa with HIV and first-line treatment failure, use of a nucleoside reverse-transcriptase inhibitor was more effective as a ritonivir-boosted protease inhibitor (lopinavir-ritonavir), and as effective as combined NRTI and lopinavir-ritonavir, in achieving good HIV control (no stage 4 events, CD4>250, viral load<10,000 copies /ml at 96 weeks of observation.

Randomised trials in child health in developing countries 2014-15

- In HIV exposed, uninfected infants in Kenya and South Africa, not breast-feeding was associated with an increased risk of serious infectious events in the first 3 months of life.

- In Zimbabwe, Nigeria, Malawi and South Africa, trials of the implementation of "Option B+", which provides all HIV-infected pregnant and breast-feeding women with lifelong combination ART, have been planned and are underway.

- In Cameroon, mobile-phone text messaging and phone call reminders increased attendance for HIV exposed or infected children.

- A controlled trial of wearing shoes failed to reduce hookworm, because those in the control arm also acquired shoes! Wearing shoes in either arm was associated with a lower risk of hookworm infection.

- Among children in Tanzania infected with Trichuris trichura, the use of albendazole and oxantel pamoate, or Albendazole and ivermectin, were more effective than the albendazole and mebendazole, or mebendazole alone.

- In India, a large trial of Integrated Management of Neonatal and Childhood Illness reduced inequity in post-neonatal mortality; that is the effect on child survival beyond the neonatal period was greatest in those from poorer families, and living within areas where IMNCI was introduced was associated with increased care seeking for neonatal illness, diarrhoea and pneumonia, and a greater chance of being breast fed for 6 months.

- Among hospitalised Indian children receiving IV fluids, with severe pneumonia or central nervous system infections, use of an isotonic fluid reduced the risk of hyponatraemia compared with use of a hypotonic fluid.

- In Ghana, providing rapid diagnostic tests for malaria along with realistic training markedly increased the prescription of rational therapy, and in Camaroon use of RDTs reduced the costs of health care in a study which helped define the best type of health worker training.

- A meta-analysis of trials of intermittent preventative therapy for malaria on the effect on anaemia showed a modest protective effect only.

- Among children in Malawi treated for malaria with chloroquine-azithromycin, the incidence of subsequent respiratory and gastrointestinal infections was lower than those treated with chloroquine alone.

- Among Ugandan children the use of dihydroartemisinin-piperaquine compared with artemether-lumefantrine reduced the risk of recurrent malaria and hospitalisations over the 84 days of follow-up.

- Among children with sickle-cell disease, malaria parasite clearance was slower than for children without SCD when treated with artemisinin-based therapies.

- In a large meta-analysis of severe malaria, arthemeter was probably less effective in reducing mortality than artesunate, although there are limited direct comparison trials.

Randomised trials in child health in developing countries 2014-15

- Among children with vivax malaria in Peru, 7 days of primaquine was as effective in preventing relapses as 14 days of primaquine.

- In a large cluster RCT of community-based treatment of moderate malnutrition in Burkina Faso, the giving of locally produced ready-to-use supplemental feeds resulted in better weight gain than merely counselling parents about appropriate foods.

- In Kenya, Mozambique and Tanzania, mothers receiving intermittent preventative therapy for malaria with mefloquine had significantly lower rates of malarial parasitaemia, placental malaria and non-obstetric hospital admissions than mothers receiving placebo, but those who received mefloquine had higher rates of perinatal mother-to-child transmission of HIV. This was an exploratory finding with potential confounding, but requires further investigation.

- In Malawi, a large trial of maternal nutrient supplementation with lipid-based nutrient supplementation failed to show improved birth size or child growth in the first 18 months of life. However in another large trial in Ghana, birth weight was greater (+85g) and risk of low birth weight less with lipid-based nutrient supplementation.

- In Argentina, a trial of delayed cord clamping showed that it was just as effective if the baby is nursed on the mother's abdomen immediately after birth as if the baby is held at the level of the placenta. That is, there is no detrimental effect on blood transfer from placental to baby of immediate skin-to-skin contact with the mother (despite the baby being higher). In India, umbilical cord milking (a quicker process that may be done in emergency situations) resulted in no different haemoglobin or serum ferritin than delayed cord clamping for 60-90 seconds.

- In a large trial in rural Tanzania, home-based counselling of newborn care practices by volunteers improved several practices, including clean cord care and exclusive breast-feeding.

- In India, the routine use of antibiotics to babies born through meconium stained amniotic fluid did not reduce the risk of sepsis.

- In 6 countries in South America, Asia and Africa, a trial of antenatal steroids fopr pregnant women at risk of preterm birth did not reduce mortality in those who delivered preterm, but increased neonatal and maternal sepsis and increased overall neonatal mortality.

- Among very low birth weight infants in Turkey, the use of probiotics (Bifidobacterium lactis) added to expressed breast-milk reduced the risk of necrotising enterocolitis, clinical nosocomial sepsis, length of NICU stay and mortality, compared with placebo or a pre-biotic (inulin).

- In DR Congo, Kenya and Nigeria, the community based treatment of low risk but possible bacterial infection in newborns with simplified antibiotic regimens which included oral amoxicillin instead of injectable penicillin were no different in effect on newborn sepsis. Similarly for infants up to 3 months of age with fast breathing only, oral amoxicillin was as effective as injectable penicillin and gentamicin. Both trials were done in populations at very low risk of serious bacterial infection.

Randomised trials in child health in developing countries 2014-15

- In a large trial in 55 villages in Burkina Faso, the implementation of an agriculture, nutrition and health behaviour program run by Helen Keller International reduced wasting, diarrhoea and anaemia.

- In a large meta-analysis of 30 trials, praziquantel was the most effective drug for treating urinary schistosomiasis, however the proportion of patients cured varied from 22-83%, and trials of combination therapy with other agents is indicated. There is still no appropriate formulation of praziquantel for young children.

- In a trial of shortened TB drug regimens, use of a 4-month regimen that included moxifloxacin was significantly less effective than the standard regimen 2RHZE/4RH. At this stage shortening TB treatment to less than 6 months is not of proven efficacy.

- In Indian children with grade I-IV vesicoureteric reflux, use of antibiotic prophylaxis with trimethoprim-sufamethoxizole was associated with a greater risk of UTI, most of which were caused by TMP-SMX resistant bacteria. Children receiving antibiotic prophyxis also had a greater risk of renal scarring.

- In a study involving over 10,000 children aged 2-14 years in 5 countries in Asia, three doses of a recombinant, live, attenuated tetravalent Dengue vaccine (CYD-DTV) was 56% efficacious in preventing symptomatic, virologically confirmed dengue over 25 months of follow-up.

- A follow-up study of HPV vaccine in Taiwan showed protective antibodies for 6 years, at levels which could be expected to last at least 20 years post vaccination.

- In South Africa, influenza vaccine given to pregnant HIV-positive and HIV-negative women provided partial protection (around 50% efficacy) for them, and protection for the infants the infants were HIV-unexposed. There was no protection of giving maternal influenza vaccine to infants who were HIV-infected or exposed.

- In 11 African sites 3 doses of the RTS,S/AS01 malaria vaccine given to infants provided 40-50% protection against clinical malaria, 34% protection against severe malaria and 19% protection against all-cause hospitalisation.

- In India, giving IPV to children who have at least 6 months previously received 3 doses of OPV boosted intestinal immunity and reduced viral excretion after exposure to a test dose of bivalent OPV. This boosted intestinal immunity may be used to prevent outbreaks of poliomyelitis.

- In Indian children given rotavirus vaccine at 6, 10 and 14 weeks, protective efficacy against rotavirus gastroenteritis and severe rotavirus disease of about 50% was observed in the second year of life.

- There were several large trials of neonatal vitamin A supplementation reported on in 2014-15, finding minimal or no effect on mortality. In a trial in India of over 40,000 newborns randomised to vitamin A 50,000 U or placebo showed a modest lower mortality (-3 per 1000, 95% CI -6% to 0.1) in the first 6 months of life, and in similar trials in Ghana and Tanzania involving 22,000 and 32,000 newborn infants respectively, the mortality risk was also not significantly different in the vitamin supplemented group. Bulging fontanelle was

reported as an adverse effect in <1% of newborns given vitamin A. Trials from Guinea Bissau confirmed no beneficial effect of neonatal vitamin A supplementation.

- In Indian children with acute respiratory infection, 2 weeks of prophylactic zinc supplementation reduced subsequent acute *lower* respiratory infections over the following 5 months of follow-up, but had no effect on all acute respiratory infections.

Again this year many studies had small sample sizes; 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 lead to the discarding of an effective intervention, or numerous inadequate trials of the same intervention.

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 may 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).

Incorporating a detailed understanding of effect in context requires a nuanced approach to clinical trials, and the randomised design may not be the best method for all interventions. This is especially the case for complex interventions (i.e. a complex clinical therapy or a health system improvement program)

In the last 13 years there have been 1995 trials summarised in the various editions of this booklet. The public health benefits that have come from the trials on malaria, for example can be seen in the uptake of new interventions and reductions in malaria in each affected country in the world. The funding of comprehensive programs of research to "roll-back" malaria and implement the results of trials is a good example of the optimum benefit of research. The changes to HIV treatment is another example of public health which has benefited remarkably from randomised trials: the improvements to prevention of parent-to-child transmission being a primary example. While malaria and HIV rates are falling reductions of similar magnitudes are not being seen in pneumonia, malnutrition or neonatal illness – and taking similar comprehensive approaches to the research agenda and to research-driven public health interventions are needed.

It is encouraging to see the increased evaluation of the developmental effects of interventions, especially in populations at risk of developmental problems such as HIV. Also encouraging is the increased trials among adolescents, and trials of school-based health and improvements in education.

Randomised trials in child health in developing countries 2014-15

In 2014-15 showed further the impact of economic transition, Western morbidities and high-technology research, with clinical trials this year from India and China on issues related to non-communicable diseases, including obesity, oral health, cancer, allergy, and modifying risk factors in childhood for adult cardiovascular disease.

More support is needed for developing public health research capacity in the poorest countries. The flourishing research output from China, India and other transitional countries is a welcome trend, but may mean that the health issues in the poorest nations with the highest child mortality burdens are over-shadowed, despite the overall increase in the number of trials. Ongoing efforts to reduce inequity in child health are especially important beyond 2015, and this will be served by appropriate research in the highest burden regions.

Trevor Duke
July 2015

Acknowledgement
Thanks to Lachan for help with editing

Acute respiratory infection

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

Treatment of pneumonia

Clin Infect Dis. 2015 Apr 15;60(8):1216-24. doi: 10.1093/cid/ciu1166. Epub 2014 Dec 30.

Oral amoxicillin versus benzyl penicillin for severe pneumonia among Kenyan children: a pragmatic randomized controlled noninferiority trial.

Agweyu A[1], Gathara D[1], Oliwa J[1], Muinga N[1], Edwards T[2], Allen E[3], Maleche-Obimbo E[4], English M[5]; Severe Pneumonia Study Group.

Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme, Nairobi, Medical Research Council Tropical Epidemiology Group, Department of Infectious Disease Epidemiology, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, United Kingdom, Department of Paediatrics and Child Health, University of Nairobi, Kenya, Health Services Unit, Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme, Nairobi Nuffield Department of Medicine, University of Oxford, United Kingdom.

BACKGROUND:

There are concerns that the evidence from studies showing noninferiority of oral amoxicillin to benzyl penicillin for severe pneumonia may not be generalizable to high-mortality settings.

METHODS:

An open-label, multicenter, randomized controlled noninferiority trial was conducted at 6 Kenyan hospitals. Eligible children aged 2-59 months were randomized to receive amoxicillin or benzyl penicillin and followed up for the primary outcome of treatment failure at 48 hours. A noninferiority margin of risk difference between amoxicillin and benzyl penicillin groups was prespecified at 7%.

RESULTS:

We recruited 527 children, including 302 (57.3%) with comorbidity. Treatment failure was observed in 20 of 260 (7.7%) and 21 of 261 (8.0%) of patients in the amoxicillin and benzyl penicillin arms, respectively (risk difference, -0.3% [95% confidence interval, -5.0% to 4.3%]) in per-protocol analyses. These findings were supported by the results of intention-to-treat analyses. Treatment failure by day 5 postenrollment was 11.4% and 11.0% and rising to 13.5% and 16.8% by day 14 in the amoxicillin vs benzyl penicillin groups, respectively. The most frequent cause of cumulative treatment failure at day 14 was clinical deterioration within 48 hours of enrollment (33/59 [55.9%]). Four patients died (overall mortality 0.8%) during the study, 3 of whom were allocated to the benzyl penicillin group. The presence of wheeze was independently associated with less frequent treatment failure.

CONCLUSIONS:

Our findings confirm noninferiority of amoxicillin to benzyl penicillin, provide estimates of risk of treatment failure in Kenya, and offer important additional evidence for policy making in sub-Saharan Africa.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4370168/pdf/ciu1166.pdf

J Antimicrob Chemother. 2014 Jul;69(7):1954-9. doi: 10.1093/jac/dku070. Epub 2014 Mar 19.

Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: a randomized controlled trial.

Vilas-Boas AL[1], Fontoura MS[1], Xavier-Souza G[1], Araújo-Neto CA[2], Andrade SC[3], Brim RV[2], Noblat L[4], Barral A[5], Cardoso MR[6], Nascimento-Carvalho CM[7]; PNEUMOPAC-Efficacy Study Group.

Federal University of Bahia School of Medicine, Salvador, Brazil; University of São Paulo School of Public Health, São Paulo, Brazil, Department of Paediatrics, Federal University of Bahia School of Medicine, Salvador, Brazil nascimentocarvalho@hotmail.com

OBJECTIVES:

Oral amoxicillin (50 mg/kg/day) thrice daily is the first-line therapy for non-severe childhood pneumonia. Compliance could be enhanced if two daily doses are employed. We assessed the equivalence of oral amoxicillin (50 mg/kg/day) thrice or twice daily in those patients.

PATIENTS AND METHODS:

This randomized (1:1), controlled, triple-blinded investigation conducted at one centre in Brazil included children aged 2-59 months with non-severe pneumonia diagnosed by trained paediatricians based on respiratory complaints and radiographic pulmonary infiltrate/consolidation. Participants were randomly assigned to receive one bottle (Amoxicillin 1) at 6 am, 2 pm and 10 pm and the other bottle (Amoxicillin 2) at 8 am and 8 pm: one bottle contained amoxicillin and the other placebo and vice versa. Only the pharmacist knew patients' allocation. Follow-up assessments were done at 2, 5 and 14 days after enrolment. Chest radiographs were read by three independent radiologists. Primary outcome was treatment failure (development of danger signs, persistence of fever, tachypnoea, development of serious adverse reactions, death and withdrawal from the trial) at 48 h.

RESULTS:

Four hundred and twelve and 408 participants received amoxicillin thrice or twice daily, respectively. Treatment failure was detected in 94 (22.8%) and 94 (23.0%) patients in intention-to-treat analysis (risk difference 0.2%; 95% CI: -5.5%-6.0%) and in 80 (20.1%) and 85 (21.3%) patients in per-protocol analysis (risk difference 1.2%; 95% CI: -4.4%-6.8%). Pneumonia was radiologically confirmed by concordant reading in 277 (33.8%) cases, among whom treatment failure was registered in 25/133 (18.8%) and 27/144 (18.8%) participants from the thrice and twice daily doses subgroups, respectively (risk difference -0.05%; 95% CI: -9.3%-9.2%).

CONCLUSIONS:

Oral amoxicillin (50 mg/kg/day) twice daily is as efficacious as thrice daily.

http://jac.oxfordjournals.org/content/69/7/1954.long

Otitis media

Am J Otolaryngol. 2014 Nov-Dec;35(6):766-70. doi: 10.1016/j.amjoto.2014.06.006. Epub 2014 Jun 20.

A double-blind randomized placebo-controlled trial of topical intranasal mometasone furoate nasal spray in children of adenoidal hypertrophy with otitis media with effusion.

Bhargava R[1], Chakravarti A[2].

Lady Hardinge Medical College, New Delhi-110001, India, dr.rahul.bhargava@gmail.com

PURPOSE:

To study the effects of topical intranasal mometasone furoate nasal spray for management of otitis media with effusion in children aged 2-12 years with adenoidal hypertrophy and its impact on change in quality of life.

METHOD:

A prospective randomized double blind interventional placebo control study was conducted. Hundred patients of endoscopic grade 3 or 4 adenoidal hypertrophy aged 2-12 years were enrolled in this study. Among these sixty two patients had persistent bilateral otitis media with effusion more than three months. These were randomly divided into two groups, group A and group B. Group A received mometasone nasal spray for six months and group B received saline nasal spray for the same period. Patients were evaluated with symptom, pure tone audiometry wherever possible, pneumatic otoscopic examination and tympanogram at 0, 8 and 24 weeks.

RESULTS:

Resolution of otitis media with effusion in study group (28 out of 30) was significantly higher as compared control group (16 out of 32) (p value 0.0004). A significant improvement in hearing and symptoms was seen in the study group ($p<0.04$). Statistically significant change in quality of life was seen with mometasone nasal spray (37.11) as compared to saline nasal spray (11.02) (p value 0.0001).

CONCLUSION:

Mometasone nasal spray appears to be effective for the treatment of otitis media with effusion in patients of adenoidal hypertrophy.

Bronchiolitis

Tunis Med. 2014 Nov;92(11):674-7.

A randomized, controlled trial of nebulized 5% hypertonic saline and mixed 5% hypertonic saline with epinephrine in bronchiolitis.

Tinsa F, Abdelkafi S, Bel Haj I, Hamouda S, Brini I, Zouari B, Boussetta K.

BACKGROUND:

Bronchiolitis is a public health problem in the word and in Tunisia. Nebulized hypertonic saline seems to have some benefits in bronchiolitis. The aim of this study is to evaluate the efficacy of nebulized 5% hypertonic saline alone or mixed with epinephrine in bronchiolitis as measured by improvement in clinical score, oxygen saturation or reduction in duration of hospitalization.

METHODS:

This prospective, double blind, placebo controlled, randomized clinical trial was performed at Children's Hospital of Tunis from February 2012 to Mars 2012. A total of 94 patients less than 12 months of age with diagnosis of moderately severe bronchiolitis were enrolled and assigned to receive 5% nebulized hypertonic saline, mixed 5% hypertonic saline with standard epinephrine 0,1% or normal saline (placebo) at admission and every 4 hours during hospitalization.

RESULTS:

There were no significant difference between nebulized 5% hypertonic saline, mixed 5% hypertonic saline with epinephrine or normal saline at baseline, T30 min, T60 min, and T120 min after start study in Wang severity score, oxygen saturation in room air, rate respiratory and heart rate. There was no difference in duration of hospitalization.

CONCLUSION:

Nebulized 5% hypertonic saline or mixed 5% hypertonic saline with epinephrine are safety but does not appear effective in treating moderately ill infants with the first acute bronchiolitis.

Upper respiratory tract infections, tonsilitis

J Altern Complement Med. 2014 Nov;20(11):868-73. doi: 10.1089/acm.2014.0189. Epub 2014 Sep 19.

Efficacy of a homeopathic complex on acute viral tonsillitis.

Malapane E[1], Solomon EM, Pellow J.

Department of Homoeopathy, University of Johannesburg , Johannesburg, South Africa

BACKGROUND:

Acute viral tonsillitis is an upper respiratory tract infection prevalent in school-aged children. Because this condition is self-limiting, conventional treatment options are usually palliative. Homeopathic remedies are a useful alternative to conventional medications in acute uncomplicated upper respiratory tract infections in children, offering earlier symptom resolution, cost-effectiveness, and fewer adverse effects. This study aimed to determine the efficacy of a homeopathic complex on the symptoms of acute viral tonsillitis in African children in South Africa.

METHODS:

This was a randomized, double-blind, placebo-controlled, 6-day pilot study. Thirty children, age 6 to 12 years, with acute viral tonsillitis were recruited from a primary school in Gauteng, South Africa. Participants took two tablets of the medication four times daily. The treatment group

received lactose tablets medicated with the homeopathic complex (Atropa belladonna D4, Calcarea phosphoricum D4, Hepar sulphuris D4, Kalium bichromat D4, Kalium muriaticum D4, Mercurius protoiodid D10, and Mercurius biniodid D10). The placebo consisted of the unmedicated vehicle only. The Wong-Baker FACES Pain Rating Scale measured pain intensity, and a Symptom Grading Scale assessed changes in tonsillitis signs and symptoms.

RESULTS:

The treatment group had a statistically significant improvement in the following symptoms compared with the placebo group: pain associated with tonsillitis, pain on swallowing, erythema and inflammation of the pharynx, and tonsil size.

CONCLUSION:

The homeopathic complex used in this study exhibited significant anti-inflammatory and pain-relieving qualities in children with acute viral tonsillitis. No patients reported any adverse effects. These preliminary findings are promising; however, the sample size was small and therefore a definitive conclusion cannot be reached. A larger, more inclusive research study should be undertaken to verify the findings of this study.

BMC Complement Altern Med. 2014 Jul 30;14:273. doi: 10.1186/1472-6882-14-273.

Chinese patent medicines for the treatment of the common cold: a systematic review of randomized clinical trials.

Chen W, Liu B, Wang LQ, Ren J, Liu JP[1].

Centre For Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China. jianping_l@hotmail.com

BACKGROUND:

Many Chinese patent medicines (CPMs) have been authorized by the Chinese State of Food and Drug Administration for the treatment of the common cold. A number of clinical trials have been conducted and published. However, there is no systematic review or meta-analysis on their efficacy and safety for the common cold to justify their clinical use.

METHODS:

We searched CENTRAL, MEDLINE, EMBASE, SinoMed, CNKI, VIP, China Important Conference Papers Database, China Dissertation Database, and online clinical trial registry websites for published and unpublished randomized clinical trials (RCTs) of CPMs for the common cold till 31 March 2013. Revman 5.2 software was used for data analysis with effect estimate presented as relative risk (RR) and mean difference (MD) with a 95% confidence interval (CI).

RESULTS:

A total of five RCTs were identified. All of the RCTs were of high risk of bias with flawed study design and poor methodological quality. All RCTs included children aged between 6 months to 14 years. Results of individual trials showed that Shuanghuanglian oral liquid (RR 4.00; 95% CI: 2.26 to 7.08), and Xiaoer Resuqing oral liquid (RR 1.43; 95% CI: 1.15 to 1.77)

had higher cure rates compared with antivirus drugs. Most of the trials did not report adverse events, and the safety of CPMs was still uncertain.

CONCLUSIONS:

Some CPMs showed a potential positive effect for the common cold on cure rate. However, due to the poor methodology quality and the defects in the clinical design of the included RCTs, such as the lack of placebo controlled trials, the inappropriate comparison intervention and outcome measurement, the confirmative conclusions on the beneficial effect of CPMs for the common cold could not be drawn.

http://www.biomedcentral.com/content/pdf/1472-6882-14-273.pdf
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4129119/pdf/12906_2013_Article_1854.pdf

Int J Pediatr Otorhinolaryngol. 2014 Sep;78(9):1526-33. doi: 10.1016/j.ijporl.2014.06.027. Epub 2014 Jul 7.

Comparison of treatment modalities in syndromic children with obstructive sleep apnea--a randomized cohort study.

Sudarsan SS[1], Paramasivan VK[2], Arumugam SV[2], Murali S[2], Kameswaran M[2].

Madras ENT Research Foundation (P) Ltd, Chennai, India. b7shyam@yahoo.com

INTRODUCTION:

Obstructive Sleep Apnea (OSA) is a common medical problem in adults that is becoming increasingly recognized in children. It occurs in the pediatric age group, from newborns to teens. More recently, many specialists have estimated OSA prevalence to be between 5 and 6%. However, in syndromic children, the prevalence of OSA can be from 50 to 100%, having a significant effect on their Quality-of-Life. As they are a challenging population for management, it is essential to evaluate them thoroughly before planning appropriate intervention.

OBJECTIVE:

To compare the efficacy of Adenotonsillectomy (T&A) and Continuous Positive Airway Pressure (CPAP) in syndromic children [Down syndrome (DS) and Mucopolysaccharidoses (MPS)] with Obstructive Sleep Apnea (OSA).

MATERIALS AND METHODS:

In a prospective, randomized, cohort comparative study, 124 syndromic children (DS and MPS) aged between 6 and 12 years were recruited from a private MPS support group and the Down Syndrome Society, Chennai. A standard assessment was performed on all children who entered the study including a full overnight Polysomnogram (PSG), Epworth Sleepiness Scale-Children (ESS-C) and Quality-of-Life (QOL) tool OSA-18. The children with positive PSG who consented for the study (n = 80) were randomly distributed to two groups, T&A group & CPAP group. The children were followed up with repeat PSG, clinical evaluation, ESS-C and Quality-of-Life (QOL) tool OSA-18 for a period of 1 year.

OBSERVATION AND RESULTS:

Follow-up was available for 73 syndromic children. Both the groups, T&A group and CPAP group, showed statistically significant ($p < 0.05$) improvement in Apnea-Hypoapnea Index (AHI), ESS-C, QOL from the intervention. In our study, T&A showed equal outcome compared to CPAP. The contrasting feature between the two groups was that CPAP use gave immediate

sustained improvement while T&A gave gradual progressive improvement of symptoms over a period of 1 year.

CONCLUSION:

On average, T&A gives equal outcomes as CPAP and it can be suggested as a first-line treatment in this group of syndromic children.

Adolescent health

(See also Vaccines - HPV vaccine and Injury prevention)

J Pak Med Assoc. 2014 Sep;64(9):987-92.

Effect of an intervention on attitudes towards domestic violence among Iranian girls.

Ekhtiari YS, Shojaeizadeh D, Foroushani AR, Ghofranipour F, Ahmadis B.

OBJECTIVE:

To evaluate the effect of an intervention based on the Precede-Proceed Model on attitudes towards prevention of Domestic Violence among Iranian girls.

METHODS:

The randomised controlled trial was conducted during 2010-11 at 10 high schools in District 17 ofTehran Municipality in Iran. The subjects were divided into two equal groups of cases and controls. Components of the Precede-Proceed Model for planning, implementation and evaluation of the study. After need assessment, an appropriate environmental and educational intervention was implemented in the intervention group. Changes in predisposing, reinforcing, enabling factors and especially attitudes towards prevention of Domestic Violence immediately and two months after the intervention were assessed in by questionnaires based on the Precede-Proceed Model. SPSS 18 was used for statistical analyses.

RESULTS:

There were 510 students who comprised the study population, with 255 individuals in each of the two groups. The intervention had significantly positive effect on predisposing, enabling and reinforcing factors immediately and two months after the intervention ($p < 0.05$). Repeated measures analysis of variance showed a significant positive increase in attitude score in the intervention group from baseline to two months ($p < 0.001$).

CONCLUSION:

The Precede-Proceed Model is one of the most widely used health planning models for identifying factors that influence health behaviours associated with domestic violence. Implementation of an educational programme based on the model among young girls was effective in changing attitude towards domestic violence.

Pediatrics. 2015 Mar;135(3):e635-43. doi: 10.1542/peds.2014-2419. Epub 2015 Feb 16.

A school-based sleep education program for adolescents: a cluster randomized trial.

Wing YK[1], Chan NY[2], Man Yu MW[2], Lam SP[2], Zhang J[2], Li SX[2], Kong AP[3], Li AM[4].

Departments of Psychiatry, Medicine and Therapeutics, and Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China.

Abstract

OBJECTIVES:

To evaluate the effectiveness of a multilevel and multimodal school-based education program.

METHODS:

A cluster randomized controlled trial with 14 secondary schools in Hong Kong and a total of 3713 students (intervention: 1545 vs control: 2168; 40.2% boys; mean age ± SD: 14.72 ± 1.53 years) were included in the final analysis. The intervention included a town hall seminar, small class workshops, a slogan competition, a brochure, and an educational Web site. Their parents and teachers were offered sleep education seminars. The control schools did not receive any sleep program. Data were collected before and 5 weeks after the intervention.

RESULTS:

The students in the intervention group had significantly improved sleep knowledge compared with the control group (mean difference: 3.64 [95% confidence interval (CI): 3.21 to 4.07]; Cohen's d = 0.51) as measured by using a sleep knowledge questionnaire. Weekday sleep duration was reduced in both groups, and the significant difference in weekday sleep duration was lost in the intention-to-treat analysis (mean difference: 0:01 [95% CI: -0:00 to 0:04]). In addition, the intervention group had a lower incidence of consuming caffeine-containing energy drinks (adjusted odds ratio: 0.46 [95% CI: 0.22 to 0.99]) and had better behavioral (mean difference: -0.56 [95% CI: -1.02 to -0.10]; Cohen's d = 0.13) and mental health (mean difference: -0.30 [95% CI: -0.15 to -0.46]; Cohen's d = 0.11) outcomes.

CONCLUSIONS:

A school-based sleep education program was effective in enhancing sleep knowledge and improving behavioral and mental health, but it had no significant impact on sleep duration or pattern among adolescents.

http://pediatrics.aappublications.org/content/135/3/e635.full.pdf

Child Abuse Negl. 2014 Jul;38(7):1197-207. doi: 10.1016/j.chiabu.2014.02.004. Epub 2014 Mar 15.

A pilot study of a family focused, psychosocial intervention with war-exposed youth at risk of attack and abduction in north-eastern Democratic Republic of Congo.

O'Callaghan P[1], Branham L[2], Shannon C[1], Betancourt TS[3], Dempster M[1], McMullen J[1].

School of Psychology, Queen's University, Belfast, Northern Ireland, UK, Discover the Journey, USA, Child Health and Human Rights, Department of Global Health and Population, Harvard School of Public Health, 651 Huntington Avenue, Boston, MA 02115, USA.

Abstract

Rural communities in the Haut-Uele Province of northern Democratic Republic of Congo live in constant danger of attack and/or abduction by units of the Lord's Resistance Army operating in the region. This pilot study sought to develop and evaluate a community-participative psychosocial intervention involving life skills and relaxation training and Mobile Cinema screenings with this war-affected population living under current threat. 159 war-affected children and young people (aged 7-18) from the villages of Kiliwa and Li-May in north-eastern DR Congo took part in this study. In total, 22% of participants had been abduction previously while 73% had a family member abducted. Symptoms of post-traumatic stress reactions, internalising problems, conduct problems and pro-social behaviour were assessed by blinded interviewers at pre- and post-intervention and at 3-month follow-up. Participants were randomised (with an accompanying caregiver) to 8 sessions of a group-based, community-participative, psychosocial intervention (n=79) carried out by supervised local, lay facilitators or a wait-list control group (n=80). Average seminar attendance rates were high: 88% for participants and 84% for caregivers. Drop-out was low: 97% of participants were assessed at post-intervention and 88% at 3 month follow-up. At post-test, participants reported significantly fewer symptoms of post-traumatic stress reactions compared to controls (Cohen's d=0.40). At 3 month follow up, large improvements in internalising symptoms and moderate improvements in pro-social scores were reported, with caregivers noting a moderate to large decline in conduct problems among the young people.

Allergy

(See Vitamin D, skin disease)

Anaemia and iron deficiency

BMC Med. 2015 Feb 2;13:21. doi: 10.1186/s12916-014-0246-7.

Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness.

Kiguli S, Maitland K[1], George EC, Olupot-Olupot P, Opoka RO, Engoru C, Akech SO, Nyeko R, Mtove G, Reyburn H, Levin M, Babiker AG, Gibb DM, Crawley J.

Kilifi Clinical Trials Facility, KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya. k.maitland@imperial.ac.uk

BACKGROUND:

Severe anaemia in children is a leading cause of hospital admission and a major cause of mortality in sub-Saharan Africa, yet there are limited published data on blood transfusion in this vulnerable group.

METHODS:

We present data from a large controlled trial of fluid resuscitation (Fluid Expansion As Supportive Therapy (FEAST) trial) on the prevalence, clinical features, and transfusion management of anaemia in children presenting to hospitals in three East African countries with serious febrile illness (predominantly malaria and/or sepsis) and impaired peripheral perfusion.

RESULTS:

Of 3,170 children in the FEAST trial, 3,082 (97%) had baseline haemoglobin (Hb) measurement, 2,346/3,082 (76%) were anaemic (Hb <10 g/dL), and 33% severely anaemic (Hb <5 g/dL). Prevalence of severe anaemia varied from 12% in Kenya to 41% in eastern Uganda. 1,387/3,082 (45%) children were transfused (81% within 8 hours). Adherence to WHO transfusion guidelines was poor. Among severely anaemic children who were not transfused, 52% (54/103) died within 8 hours, and 90% of these deaths occurred within 2.5 hours of randomisation. By 24 hours, 128/1,002 (13%) severely anaemic children had died, compared to 36/501 (7%) and 71/843 (8%) of those with moderate and mild anaemia, respectively. Among children without severe hypotension who were randomised to receive fluid boluses of 0.9% saline or albumin, mortality was increased (10.6% and 10.5%, respectively) compared to controls (7.2%), regardless of admission Hb level. Repeat transfusion varied from ≤2% in Kenya/Tanzania to 6 to 13% at the four Ugandan centres. Adverse reactions to blood were rare (0.4%).

CONCLUSIONS:

Severe anaemia complicates one third of childhood admissions with serious febrile illness to hospitals in East Africa, and is associated with increased mortality. A high proportion of deaths occurred within 2.5 hours of admission, emphasizing the need for rapid recognition and prompt blood transfusion. Adherence to current WHO transfusion guidelines was poor. The high rates of re-transfusion suggest that 20 mL/kg whole blood or 10 mL/kg packed cells may undertreat a significant proportion of anaemic children. Future evaluation of the impact of a larger volume of transfused blood and optimum transfusion management of children with Hb of <6 g/dL is warranted.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4313469/pdf/12916_2014_Article_246.pdf

J Nutr. 2014 Nov;144(11):1703-9. doi: 10.3945/jn.114.193417. Epub 2014 Sep 3.

Inhibition of iron absorption by calcium is modest in an iron-fortified, casein- and whey-based drink in Indian children and is easily compensated for by addition of ascorbic acid.

Walczyk T[1], Muthayya S[2], Wegmüller R[3], Thankachan P[2], Sierksma A[4], Frenken LG[4], Thomas T[2], Kurpad A[2], Hurrell RF[3].

Laboratory for Human Nutrition, Swiss Federal Institute of Technology (ETH) Zurich, Zurich, Switzerland; Departments of Chemistry (Science) and Biochemistry (Medicine), National University of Singapore, Singapore; Division of Nutrition, St. John's Research Institute, Bangalore, India; and Laboratory for Human Nutrition, Swiss Federal Institute of Technology (ETH) Zurich, Zurich, Switzerland; [4]Unilever Research and Development, Vlaardingen, The Netherlands.

BACKGROUND:

Calcium inhibits and ascorbic acid (AA) enhances iron absorption from iron-fortified foods. Absorption efficiency depends on iron status, although the interaction is unclear.

OBJECTIVE:

We investigated the ability of AA to overcome calcium-induced inhibition of iron absorption in children differing in iron status.

METHODS:

The effect of calcium (0, 100, and 200 mg/test meal) on iron absorption in the absence and presence of AA (0, 42.5, and 85 mg/test meal) from a casein/whey-based drink fortified with ferrous sulfate was assessed in a series of randomized crossover studies both in iron-replete (IR) Indian schoolchildren and in children with iron deficiency anemia (IDA) (6-11 y; n = 14-16/group) by using stable isotopes.

RESULTS:

In the absence of calcium and AA, iron absorption from the casein/whey-based drink was 20% lower in IR children than in children with IDA. The addition of calcium reduced mean iron absorption by 18-27%, with the effect being stronger for high added calcium ($P < 0.01$). AA at a 2:1 or 4:1 molar ratio enhanced iron absorption by a factor of 2-4 and greatly overcompensated for the inhibitory effect of calcium on iron absorption in a dose-dependent manner ($P < 0.001$). The dose-response effect tended to be stronger ($P < 0.1$) in the IDA group, and iron status was of far less influence on iron absorption than the enhancing effect of AA.

CONCLUSION:

When adding AA to iron-fortified milk products, care should be taken not to provide absorbable iron in excess of needs.

Br J Nutr. 2014 Aug 28;112(4):547-56. doi: 10.1017/S0007114514001160. Epub 2014 Jun 11.

Effects of iron supplementation on dominant bacterial groups in the gut, faecal SCFA and gut inflammation: a randomised, placebo-controlled intervention trial in South African children.

Dostal A[1], Baumgartner J[2], Riesen N[1], Chassard C[1], Smuts CM[3], Zimmermann MB[2], Lacroix C[1].

Institute of Food, Nutrition and Health,ETH Zurich, Switzerland; Centre of Excellence for Nutrition, North-West University, Potchefstroom Campus,South Africa.

Abstract

Fe supplementation is a common strategy to correct Fe-deficiency anaemia in children; however, it may modify the gut microbiota and increase the risk for enteropathogenic infection. In the present study, we studied the impact of Fe supplementation on the abundance of dominant bacterial groups in the gut, faecal SCFA concentration and gut inflammation in children living in rural South Africa. In a randomised, placebo-controlled intervention trial of 38 weeks, 6- to 11-year-old children with Fe deficiency received orally either tablets containing 50 mg Fe as $FeSO_4$ (n 22) for 4 d/week or identical placebo (n 27). In addition, Fe-sufficient children (n 24) were included as a non-treated reference group. Faecal samples were analysed at baseline and at 2, 12 and 38 weeks to determine the effects of Fe supplementation on ten bacterial groups in the gut (quantitative PCR), faecal SCFA concentration (HPLC) and gut inflammation (faecal calprotectin concentration). At baseline, concentrations of bacterial groups in the gut, faecal

SCFA and faecal calprotectin did not differ between Fe-deficient and Fe-sufficient children. Fe supplementation significantly improved Fe status in Fe-deficient children and did not significantly increase faecal calprotectin concentration. Moreover, no significant effect of Fe treatment or time × treatment interaction on the concentrations of bacterial groups in the gut or faecal SCFA was observed compared with the placebo treatment. Also, there were no significant differences observed in the concentrations of any of the bacterial target groups or faecal SCFA at 2, 12 or 38 weeks between the three groups of children when correcting for baseline values. The present study suggests that in African children with a low enteropathogen burden, Fe status and dietary Fe supplementation did not significantly affect the dominant bacterial groups in the gut, faecal SCFA concentration or gut inflammation.

Nutrition. 2014 Jul-Aug;30(7-8):771-5. doi: 10.1016/j.nut.2013.12.008. Epub 2013 Dec 15.

Reducing iron deficiency anemia in Bolivian school children: calcium and iron combined versus iron supplementation alone.

Miranda M[1], Olivares M[1], Brito A[2], Pizarro F[3].

Micronutrients Laboratory, Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile; U.S. Department of Agriculture, Western Human Nutrition Research Center, University of California, Davis, California, USA.

OBJECTIVE:

The aim of this study was to determine the effect of combined calcium and iron versus single iron supplementation on iron status in Bolivian schoolchildren.

METHODS:

Children ages 6 to 10 y old (N = 195), were randomly assigned to receive either 700 mg Ca (as calcium carbonate) plus 30 mg Fe (as ferrous sulfate) (Ca + Fe group) or 30 mg Fe (as ferrous sulfate) (Fe group). The doses were administered daily, from Monday to Friday, between meals at school over 3 mo. Iron status was assessed at baseline and after intervention. Additionally, overall nutritional status was assessed by anthropometry and an estimation of dietary intake.

RESULTS:

At baseline, the prevalence of anemia in the Ca + Fe group and the Fe group were 15% and 21.5%, respectively. After 3 mo follow-up, the prevalence of iron deficiency anemia dropped significantly ($P < 0.001$) to 3% in both groups ($\chi(2) = NS$). Iron dietary intake was within recommended levels, but calcium intake only covered 39% of the Recommended Daily Intake.

CONCLUSION:

Combined calcium and iron supplementation is equally as effective as single iron supplementation in reducing the prevalence of iron deficiency anemia in Bolivian school children.

Am J Clin Nutr. 2015 Mar;101(3):668-79. doi: 10.3945/ajcn.113.081208. Epub 2014 Dec 31.

n-3 Long-chain PUFAs reduce respiratory morbidity caused by iron supplementation in iron-deficient South African schoolchildren: a randomized, double-blind, placebo-controlled intervention.

Malan L[1], Baumgartner J[1], Calder PC[1], Zimmermann MB[1], Smuts CM[1].

Centre of Excellence for Nutrition, North-West University, Potchefstroom, South Africa (LM, CMS, and JB); the Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom (PCC), the National Institute for Health Research Biomedical Research Centre in Nutrition, Southampton University Hospital National Health Service Foundation Trust and University of Southampton, Southampton, United Kingdom (PCC); the Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia (PCC); and the Laboratory of Human Nutrition, Institute of Food, Nutrition and Health, Eidgenössische Technische Hochschule Zürich, Switzerland (MBZ).

BACKGROUND:

Although iron supplementation in malaria-free areas mostly reduces infectious morbidity, it can sometimes increase morbidity from infections as a result of the dependence of pathogenic microorganisms on iron. Supplementation with n-3 (ω-3) long-chain polyunsaturated fatty acids (LCPUFAs) improved morbidity in several human studies. However, information on the combined effect of iron and n-3 LCPUFA supplementation on infectious morbidity is limited.

OBJECTIVE:

We determined whether n-3 LCPUFAs and iron supplementation, alone or in combination, affected absenteeism and illness in iron-deficient schoolchildren with low fish intake.

DESIGN:

A total of 321 South African children (aged 6-11 y) with iron deficiency (ID) were randomly divided into 4 groups to receive 1) iron plus placebo, 2) a mixture of docosahexaenoic acid and eicosapentaenoic acid (DHA/EPA) plus placebo, 3) iron plus DHA/EPA, or 4) placebo plus placebo as oral supplements 4 times/wk for 8.5 mo. Morbidity was recorded, and iron-status indexes were measured. The total phospholipid fatty acid composition of peripheral blood mononuclear cell membranes was analyzed in a subsample (n = 130).

RESULTS:

Iron supplementation increased the number of days with illness when all symptoms were considered (B: 0.87; 95% CI: 0.71, 1.03) as well as illness that was specifically caused by respiratory symptoms (B: 1.45; 95% CI: 1.21, 1.70), whereas DHA/EPA reduced the number of days with illness at school (B: -0.96; 95% CI: -1.33, -0.59). The increases caused by iron were reduced to the levels seen in the placebo plus placebo group when iron was provided in combination with DHA/EPA as indicated by significant iron × DHA/EPA interactions (both $P < 0.001$).

CONCLUSION:

Iron supplementation increased morbidity (mostly respiratory) in iron-deficient South African schoolchildren with low DHA/EPA intake, but when iron was given in combination with DHA/EPA, this effect was prevented.

http://ajcn.nutrition.org/content/101/3/668.full.pdf+html

Pediatr Blood Cancer. 2015 Mar;62(3):409-13. doi: 10.1002/pbc.25349. Epub 2014 Dec 2.

The hemoglobin values of Korean adolescents show distinctive characteristics in comparison to those of Caucasians and African Americans.

Lim JS[1], Seo JH, Kim DH, Lee JA.

Department of Pediatrics, Korea Cancer Center Hospital, Seoul, Republic of Korea.

BACKGROUND:

Hematologic reference values vary by ethnicity. We aimed to determine reference values of hemoglobin (Hb) for Korean adolescents.

METHODS:

Using data from the 5th Korean National Health and Nutrition Examination Survey (KNHANES), we obtained reference values for Hb in adolescents aged 10-20 years.

RESULTS:

Among 2,526 subjects recruited, 330 were excluded due to chronic diseases (9 congenital heart disease, 6 epilepsy, and 1 thyroid disease) or abnormal laboratory values (253 subjects with Fe/TIBC <16%, 103 subjects with MCV <80 fl). Accordingly, data from 2,196 subjects (male = 1,196 and female = 1,000) were analyzed and age- and gender-stratified means and percentile values of Hb were obtained. Pertinent findings observed in the current study were: (i) Hb levels in Korean male were similar to those of non-Hispanic Caucasians; (ii) Hb values in females were similar to those of non-Hispanic Caucasians until age of 15, and thereafter were slightly lower. Prevalence of anemia according to WHO criteria and our own criteria (Hb levels <2 standard deviations of age- and gender-specific values) in total sample was 3.5% (88/2,526) and 3.8% (97/2,526), respectively. Anemia was more prevalent in female in comparison with male (6.5% vs. 1.0%, $P < 0.001$).

CONCLUSIONS:

Our results could be used as a national reference standard to correctly classify a large population sample. Further studies are necessary to determine reference Hb values for children younger than 10 years and identify genetic variations associated with distinctive characteristics observed in this study.

http://onlinelibrary.wiley.com/doi/10.1002/pbc.v62.3/issuetoc

Anaesthesia and intensive care

Anesth Analg. 2015 Feb;120(2):411-9. doi: 10.1213/ANE.0000000000000557.

Excess costs and length of hospital stay attributable to perioperative respiratory events in children.

Oofuvong M[1], Geater AF, Chongsuvivatwong V, Chanchayanon T, Sriyanaluk B, Saefung B, Nuanjun K.

Department of Anesthesiology and Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand.

BACKGROUND:

Knowledge of the excess hospital costs and prolonged length of stay attributable to perioperative respiratory event (PRE) in pediatric anesthesia is useful for hospital planning. In this study, we compared costs (excess hospital costs and indirect costs) and length of hospital stay between children who had PRE and did not have PRE for noncardiac surgery at a tertiary care hospital in southern Thailand.

METHODS:

A prospective matched cohort study was conducted in children aged <15 years who underwent general anesthesia between November 2012 and December 2013 at Songklanagarind Hospital. PRE children were matched with no PRE children (1:1) using a random selection procedure on outpatients/inpatients, type of surgery, surgical charge (baht), ASA physical status, age difference <9 years, and difference in time of surgery <6 months. Primary end points were excess hospital costs and number of days hospitalized after surgery. Number of days hospitalized after surgery, excess hospital costs and indirect costs regarding transportation, and income loss of parents between groups were compared using Wilcoxon signed rank test. Any hospital stay after surgery between groups was compared using McNemar χ test. A hurdle model was used to predict any hospital stay and number of days hospitalized after surgery. Multiple mixed-effects linear regression was used to identify predictors of adjusted excess hospital costs and indirect costs.

RESULTS:

A total 430 children were included (215 matched pairs). More PRE children required hospital stay after surgery (81% vs 72%, P = 0.004), and PRE children had a longer number of days hospitalized after surgery (median [interquartile ranges]: 1 [1-3.5] vs 1 [0-2]; P < 0.001) and incurred higher excess costs (P < 0.001) but not indirect costs (P = 0.23). In multivariate analysis, PRE was a significant predictor for hospital stay after surgery (odds ratio, 2.56; 95% confidence interval, 1.23-5.31), longer hospitalization (count ratio, 2.10 [1.31-3.35]), higher excess costs (cost ratio, 1.30 [1.12-1.53]), and indirect cost (cost ratio, 1.58 [1.20-2.08]) after adjusting for patient and anesthesia characteristics. Universal coverage (74%) was associated with 35% and 64% higher excess cost compared with the Comptroller General's Department (17%) and self-pay (7%), respectively (P = 0.003).

CONCLUSIONS:

The effects of PRE in pediatric anesthesia were hospital stay after surgery, 2 times longer hospitalization, 30% higher excess hospital costs, and 58% higher indirect cost among outpatients. Hospital policy to efficiently manage hospital beds and compensatory budget should be developed.

http://journals.lww.com/anesthesia-analgesia/pages/articleviewer.aspx?year=2015&issue=02000&article=00019&type=abstract

Intensive Care Med. 2014 Sep;40(9):1285-94. doi: 10.1007/s00134-014-3358-9. Epub 2014 Jun 18.

Dexamethasone pretreatment for 24 h versus 6 h for prevention of postextubation airway obstruction in children: a randomized double-blind trial.

Baranwal AK[1], Meena JP, Singhi SC, Muralidharan J.

Department of Pediatrics, All India Institute of Medical Sciences, Patna, 801505, India

PURPOSE:

Multidose steroid pretreatment is effective in preventing postextubation airway obstruction (PEAO) in adults, however controversy continues for children. This study was designed as a randomized, placebo-controlled, double-blind trial to compare the effect of 24-h pretreatment with dexamethasone (24hPD) versus 6-h pretreatment (6hPD) on PEAO and reintubation in children at a tertiary care hospital in a developing economy.

METHODS:

Hundred twenty-four children (3 months to 12 years) intubated for ≥48 h and planned to have extubation during next 24 h were randomized to receive 24hPD (0.5 mg/kg/dose, q6h, total of six doses; n = 66) or 6hPD (total of three doses; n = 58). Patients with preexistent upper airway conditions, chronic respiratory diseases, steroid therapy in last 7 days, gastrointestinal bleeding, hypertension, and hyperglycemia and those likely to have poor airway reflexes were excluded.

RESULTS:

The two groups were similar at baseline. 24hPD reduced the incidence of PEAO (43/66 versus 48/58; p = 0.027) with absolute risk reduction of 17 %. It also reduced the incidence of reintubation, though nonsignificantly, by half [5/61 versus 9/58; relative risk (RR), 1.09; 95 % confidence interval (CI), 0.96-1.25]. Time to recovery from PEAO among non-reintubated patients was shorter among 24hPD patients (p = 0.016). No adverse event was noted with dexamethasone use. Intubation duration >7 days and cuffed tracheal tubes were found to be independent risk factors for PEAO (odds ratio 6 and 3.12, respectively).

CONCLUSIONS:

24-h pretreatment with multidose dexamethasone reduced the incidence of PEAO and the time to recover from it. 24hPD should be considered for high-risk children intubated for >48 h in the study setting. Further studies with larger sample size from different socioeconomic background are desirable to validate these findings.

Paediatr Anaesth. 2015 Apr 27. doi: 10.1111/pan.12663. [Epub ahead of print]

Comparison of air-Q and Ambu Aura-i for controlled ventilation in infants: a randomized controlled trial.

Darlong V[1], Biyani G, Baidya DK, Pandey R, Chandralekha, Punj J, Upadhyay AD.

Department of Anesthesiology, All India Institute of Medical Sciences, New Delhi, India.

BACKGROUND:

The air-Q is a new supraglottic airway device (SAD) and has been increasingly used as a primary airway device and as a conduit for tracheal intubation in children as well as in adults. This device has either performed equally or better than other SADs in children. The Ambu Aura-i is a commonly used SAD in children undergoing various short surgical procedures. However, limited literature is available evaluating the safety and efficacy of the air-Q and the Ambu Aura-i in small children. We, therefore, conducted this study to compare the clinical performance of these two airway devices in infants weighing up to 10 kg. Our hypothesis is that air-Q, due to its improved and larger cuff design will yield better airway seal pressures as compared with the Ambu Aura-i.

METHODS:

Sixty-four ASA I-II infants weighing <10 kg undergoing elective ophthalmic surgery were randomly assigned to receive either an air-Q or the Ambu Aura-i. After induction of general anesthesia (GA) and muscle relaxation, we measured oropharyngeal leak pressure (OLP) as the primary outcome. The secondary end points measured were time to insert, first insertion success rate, fiberoptic grade (FO) of laryngeal view and any other airway complications like trauma, laryngospasm, and desaturation.

RESULTS:

The air-Q ILA provided significantly higher OLP as compared with the Ambu Aura-i [20.2 ± 4.6 cm H_2 O, CI 18.55-21.88; vs 16.2 ± 5.6 cmH_2 O, CI 14.27-18.25, P = 0.003; mean difference 4 ± 1.29 cm H_2 O, CI 1.41-6.58]. However, the Ambu Aura-i required significantly less time for its insertion (14.6 ± 2.8 s, CI 13.66-15.70; vs 16.3 ± 1.5 s, CI 15.75-16.86, P = 0.005; mean difference 1.625 ± 0.56 s, CI 0.48-2.76). There were no differences in first insertion success rate, FO view, and postoperative complications.

CONCLUSION:

We conclude that air-Q may be considered superior to Ambu Aura-i in infants for controlled ventilation as it provides higher airway sealing pressures.

Int J Clin Pediatr Dent. 2014 Sep-Dec;7(3):153-6. doi: 10.5005/jp-journals-10005-1255. Epub 2015 Feb 9.

Acceptability and Efficacy of Commercial Oral Preparation of Midazolam for brief Painful Procedure: A Randomized Double Blind Clinical Trial.

Srivastava B[1], Mittal N[2], Mittal P[3].

Department of Pedodontics and Preventive Dentistry, Santosh Dental College and Hospital, Ghaziabad, Uttar Pradesh, India.

AIM:

To compare the acceptability and efficacy of orally administered commercially available midazolam syrup and injection midazolam mixed in honey for performing venepuncture.

MATERIALS AND METHODS:

This double blind randomized controlled trial enrolled 40 anxious and healthy 2 to 6 years olds. All subjects received either syrup midazolam or injection midazolam mixed in honey (0.5 mg/kg) per orally, prior to venepuncture as per their group assignment. Primary outcome measures in this trial was acceptability of midazolam. Secondary outcome measures included sedation depth, success of venepuncture, observer and parental satisfaction and parental perception of child's pain.

RESULTS:

Although the acceptability of syrup midazolam (95%) was higher than injection midazolam (80%), there was no significant difference among two groups with respect to any primary or secondary outcome ($p > 0.05$).

CONCLUSION:

Syrup midazolam can serve as a suitable alternative to injection midazolam; thus, eliminating the procedural steps of mixing injection midazolam with any vehicle.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4335103/pdf/ijcpd-07-153.pdf

Paediatr Anaesth. 2014 Nov;24(11):1158-63. doi: 10.1111/pan.12478. Epub 2014 Jul 12.

A dose-response study of caudal dexmedetomidine with ropivacaine in pediatric day care patients undergoing lower abdominal and perineal surgeries: a randomized controlled trial.

Bharti N[1], Praveen R, Bala I.

Department of Anesthesia and Intensive Care, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

OBJECTIVES:

This randomized double-blind study was conducted to evaluate the analgesic efficacy and safety of addition of three different doses of dexmedetomidine in caudal ropivacaine compared with plain ropivacaine for postoperative analgesia in pediatric day care patients.

METHODS:

Eighty children of American Society of Anesthesiologists grade I-II, aged 1-8 years, undergoing lower abdominal and perineal surgery were included. Children were randomly allocated into four groups. Group 1 received 0.2% plain ropivacaine 0.75 ml·kg(-1), while group 2, 3, and 4 received dexmedetomidine 0.5, 1.0, and 1.5 μg·kg(-1), respectively, along with 0.2% ropivacaine 0.75 ml·kg(-1). Anesthesia was induced and maintained with sevoflurane and 50% N2O in oxygen. Children were observed for postoperative pain, nausea-vomiting, agitation, sedation, and adverse effects. Rescue analgesia was provided with oral paracetamol.

RESULTS:

Postoperative analgesia was significantly prolonged in all dexmedetomidine groups as compared to plain ropivacaine group ($P < 0.001$). All patients in the plain ropivacaine group required rescue analgesia within first 6 postoperative hours, while none in the other three groups. None of the patients showed delayed anesthetic emergence. Four patients in the plain ropivacaine group developed agitation, while none in the dexmedetomidine groups. Patients receiving dexmedetomidine 1.5 μg·kg(-1) were more sedated as compared to the other groups ($P < 0.01$), but it did not delay discharge of the patients.

CONCLUSIONS:

All three doses of caudal dexmedetomidine appear to be effective for preventing postoperative pain in pediatric day care patients. Caudal dexmedetomidine used in these doses seems to be safe for day care surgery.

http://onlinelibrary.wiley.com/doi/10.1111/pan.12478/abstract

J Med Assoc Thai. 2014 Nov;97(11):1171-6.

Comparison of minimal fresh gas requirements of baby enclosed afferent reservoir and Jackson Rees anesthetic circuit for general anesthesia in spontaneously breathing children.

Theerapongpakdee S, Sathitkamrnmanee T, Tribuddharat S, Rojanapithayakorn N, Uppan K, Thongrong C, Bunsangcharoen P.

OBJECTIVE:

The authors compared the baby enclosed afferent reservoir (Baby EAR) with the Jackson-Rees (JR) anesthesia circuit for the minimal fresh gas flow (FGF) requirement with no and clinically acceptable rebreathing in spontaneous breathing anesthesia among pediatric patients.

MATERIAL AND METHOD:

The present study was a randomized crossover study. Twenty patients, weighing 5 to 20 kg with ASA physical status I-II were enrolled. They were allocated to group 1 (EAR-JR) starting with Baby EAR then switching to JR or group 2 (JR-EAR), reversedpattern. After induction and intubation, anesthesia was maintainedwith a N2O/O2 combination with sevoflurane 1 to 3% and fentanyl. Starting with the first circuit, all patients were spontaneously ventilated with FGF 500 mL/kg/min for 10 minutes, and then gradually decreased by 50 mL/kg/min every five minutes. End-tidal CO2 (ETCO) and inspired minimum CO2 (imCO) were recorded until rebreathing (imCO2 >2 mmHg) occurred and continued until rebreathing was not clinically acceptable (imCO2 >6 mmHg). The anesthesia breathing circuit was switched and the procedure repeated.

RESULTS:

The minimal FGF at no rebreathing of Baby EAR and JR were 192.5±76.6 and 347.5±108.2 mL/kg/min; p<0.001. At acceptable rebreathing, the values were 117.5±46.7 and 227.6±90.6 mL/kg/min; p< 0. 001.

CONCLUSION:

Baby EAR can be used safely, effectively, and requires less FGF than JR in pediatric anesthesia in patients weighing 5 to 20 kg.

Intensive care

(See also: Treatment of severe malaria; Intravenous fluids)

Crit Care Med. 2014 Aug;42(8):1775-87. doi: 10.1097/CCM.0000000000000298.

Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children.

Kumar R[1], Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A.

Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

OBJECTIVE:

In children with acute CNS infection, management of raised intracranial pressure improves mortality and neuromorbidity. We compared cerebral perfusion pressure-targeted approach with the conventional intracranial pressure-targeted approach to treat raised intracranial pressure in these children.

DESIGN:

Prospective open-label randomized controlled trial.

SETTING:

PICU in a tertiary care academic institute.

PATIENTS:

Hundred ten children (1-12 yr) with acute CNS infections having raised intracranial pressure and a modified Glasgow Coma Scale score less than or equal to 8 were enrolled.

INTERVENTIONS:

Patients were randomized to receive either cerebral perfusion pressure-targeted therapy (n = 55) (maintaining cerebral perfusion pressure ≥ 60 mm Hg, using normal saline bolus and vasoactive therapy-dopamine, and if needed noradrenaline) or intracranial pressure-targeted therapy (n = 55) (maintaining intracranial pressure < 20 mm Hg using osmotherapy while ensuring normal blood pressure). The primary outcome was mortality up to 90 days after discharge from PICU. Secondary outcome was modified Glasgow Coma Scale score at 72 hours after enrollment, length of PICU stay, duration of mechanical ventilation, and hearing deficit and functional neurodisability at discharge and 90-day follow-up.

MEASUREMENTS AND MAIN RESULTS:

A 90-day mortality in intracranial pressure group (38.2%) was significantly higher than cerebral perfusion pressure group (18.2%; relative risk = 2.1; 95% CI, 1.09-4.04; p = 0.020). The cerebral perfusion pressure group in comparison with intracranial pressure group had significantly higher median (interquartile range) modified Glasgow Coma Scale score at 72 hours (10 [8-11] vs 7 [4-9], p < 0.001), shorter length of PICU stay (13 d [10.8-15.2 d] vs. 18 d [14.5-21.5 d], p = 0.002) and mechanical ventilation (7.5 d [5.4-9.6 d] vs. 11.5 d [9.5-13.5 d], p = 0.003), lower prevalence of hearing deficit (8.9% vs 37.1%; relative risk = 0.69; 95% CI, 0.53-0.90; p = 0.005), and neurodisability at discharge from PICU (53.3% vs. 82.9%; relative risk = 0.37; 95% CI, 0.17-0.81; p = 0.005) and 90 days after discharge (37.8% vs. 70.6%; relative risk = 0.47; 95% CI, 0.27-0.83; p = 0.004).

CONCLUSION:

Cerebral perfusion pressure-targeted therapy, which relied on more frequent use of vasopressors and lesser use of hyperventilation and osmotherapy, was superior to intracranial pressure-targeted therapy for management of raised intracranial pressure in children with acute CNS infection in reducing mortality and morbidity.

Intensive Care Med. 2015 Apr;41(4):677-85. doi: 10.1007/s00134-015-3694-4. Epub 2015 Feb 24.

Probiotic prophylaxis to prevent ventilator associated pneumonia (VAP) in children on mechanical ventilation: an open-label randomized controlled trial.

Banupriya B[1], Biswal N, Srinivasaraghavan R, Narayanan P, Mandal J.

Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, 605006, India.

PURPOSE:

Ventilator associated pneumonia (VAP) is one of the most common nosocomial infections in the pediatric intensive care unit (PICU). It is associated with increased mortality and prolonged hospital stay. Several preventive strategies have been introduced to reduce VAP. One novel intervention is prophylactic administration of probiotics. Studies on the effect of probiotics on VAP in pediatric populations are lacking.

METHODS:

This was an open-label randomized controlled trial. A total of 150 children no older than 12 years admitted to the PICU were recruited from November 2011 to July 2013. Children who were likely to require ventilation for more than 48 h were eligible for inclusion in the study. Patients were randomized into two groups after stratification based on age groups. Children in the intervention group received probiotic preparation twice a day beginning from the day of ICU admission till 7 days or discharge from ICU, whichever was earlier. The control group did not receive any placebo. Children were examined daily for evidence of VAP and were followed up till discharge from hospital. Incidence of VAP, duration of hospital stay, and mortality were compared.

RESULTS:

Children who received prophylactic probiotics had a lower incidence of VAP compared to the control group (17.1 % in the probiotics group vs 48.6 % in the control group, $p < 0.001$; 22 per 1,000 ventilated days vs 39 per 1,000 ventilated days, $p = 0.02$). On multiple logistic regression analysis, use of prophylactic probiotics decreased the incidence of VAP by 77 % and reduced the duration of ICU and hospital stays by an average of 2.1 and 3.3 days, respectively, after adjusting for the other confounders. No complications due to administration of probiotics were observed in the study.

CONCLUSION:

Prophylactic probiotics administration resulted in reduction of the incidence of VAP in critically ill children in a setting where baseline VAP rates are high. The intervention was found to be safe.

http://link.springer.com/article/10.1007/s00134-015-3694-4/fulltext.html

Asthma and chronic lung disease

Respir Care. 2015 Jun 16. pii: respcare.03213. [Epub ahead of print]

A Randomized Controlled Trial of 2 Inhalation Methods When Using a Pressurized Metered Dose Inhaler With Valved Holding Chamber.

Stephen D[1], Vatsa M[2], Lodha R[3], Kabra SK[3].

College of Nursing and Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

BACKGROUND:

Information on the comparative efficacy of single deep breathing versus tidal breathing for inhaled asthma medications is limited, although such information can be of much use for the treatment of patients suffering from asthma. The objective of the present study was to compare the relative difference in improvement in peak expiratory flow (PEF) with single maximal inhalation with breath-holding versus 5 tidal breaths during inhalation of salbutamol from a pressurized metered dose inhaler (pMDI) with valved holding chamber (VHC) in children 5-15 y of age with asthma.

METHODS:

The randomized controlled trial was carried out on children with asthma between 5 and 15 y of age using a pMDI with a VHC either by a single deep breath with breath-hold or 5 tidal breaths. The experimental group received 200 μg of salbutamol from the pMDI with VHC with a single maximal inhalation and breath-hold technique, whereas the control group received 200 μg of salbutamol from pMDI with VHC using the 5 tidal breaths technique. The outcome variable, PEF, was reassessed 30 min after salbutamol use.

RESULTS:

Eighty-two subjects (mean age 8.79 ± 2.5 y, 65 boys and 17 girls) were analyzed. There was significant improvement in the PEF, from baseline (pre-intervention) to post-intervention within the single maximal inhalation with breath-hold group and tidal breathing group independently ($P < .001$). The mean difference in improvement in PEF between the single maximal inhalation with a breath-hold and 5 tidal breaths group was 30.0 ± 18.16 and 28.29 ± 13.94 L/min, respectively, and was not statistically significant ($P = .88$).

CONCLUSIONS:

Single maximal inhalation with a breath-hold technique is not superior to tidal breathing for improvement in PEF following salbutamol inhalation. Either method may be used in children between 5 and 15 y of age.

Indian J Pediatr. 2014 Jul;81(7):655-9. doi: 10.1007/s12098-013-1334-y. Epub 2014 Feb 21.

Montelukast versus budesonide as a first line preventive therapy in mild persistent asthma in 2 to 18 y.

Shah MB[1], Gohil J, Khapekar S, Dave J.

Department of Pediatrics, Sir T. Hospital and Government Medical College, Bhavnagar, Gujarat, 364001, India, drmonil_shah1@yahoo.co.in

OBJECTIVES:

To compare the efficacy of oral Montelukast and inhaled Budesonide as a first line preventive therapy in mild persistent asthma in age group 2-18 y.

METHODS:

This prospective randomized controlled clinical study was conducted for 12 wk. Sixty patients of mild persistent asthma aged 2 to 18 y were randomly allocated to either oral Montelukast (n = 60) or inhaled Budesonide (n = 60) group. Outcomes measured were improvement in peak expiratory flow rate (PEFR), forced expiratory volume 1 s/forced vital capacity (FEV1/FVC), day time and night time symptoms and frequency of exacerbations and need to change medications.

RESULTS:

There was significant improvement in PEFR, FEV1/FVC, day time and night time symptoms and frequency of exacerbations in both groups. However, more significant improvement in FEV1/FVC (CI 95 %, p = 0.029) and day time symptoms (CI 95 %, p = 0.002) was seen in Budesonide group compared to Montelukast group.

CONCLUSIONS:

The present study suggests that oral Montelukast is not inferior to Budesonide in treatment of mild persistent asthma in 2 to 18 y children in terms of control of symptoms and improvement in pulmonary function tests over a 12 wk period. However, there was more significant improvement in day time symptoms, more significant increase in FEV1/FVC ratio and less exacerbation in patients receiving Budesonide compared to those receiving Montelukast. However, side effects due to long term use of steroids such as growth stunting and bone osteopenia should also be considered before recommending. Trial registered at CTRI no. REF/2012/09/004035.

Ann Allergy Asthma Immunol. 2014 Oct;113(4):404-9. doi: 10.1016/j.anai.2014.07.005. Epub 2014 Aug 3.

The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma.

Arshi S[1], Fallahpour M[2], Nabavi M[1], Bemanian MH[1], Javad-Mousavi SA[3], Nojomi M[4], Esmaeilzadeh H[1], Molatefi R[1], Rekabi M[1], Jalali F[1], Akbarpour N[1].

Department of Allergy, Department of Pulmonology, Department of Community and Preventive Medicine, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.

BACKGROUND:

Vitamin D is hypothesized to have some roles in innate and adaptive immunity, inflammation reduction, and remodeling; therefore, it is supposed to affect the asthma phenotype, severity, and response to inhaled corticosteroid (ICS).

OBJECTIVE:

To explore the synergistic effects of vitamin D supplementation in addition to asthma controllers (ICS or ICS plus long-acting β-agonist) on airway functions.

METHODS:

A randomized clinical trial was conducted in 130 individuals aged 10 to 50 years who lived in Tehran during a 24-week period. Data on age, sex, body mass index, stage of asthma, serum

total IgE, history of allergic rhinitis, atopic dermatitis, food allergy, and urticaria were collected. Spirometric parameters (forced expiratory volume in 1 second [FEV1] and ratio of FEV1 to forced vital capacity) and serum vitamin D measurement were obtained before and 8 and 24 weeks after the intervention. Patients were divided in 2 groups randomly. Both groups received asthma controllers (budesonide or budesonide plus formoterol) according to their stage, but the intervention group received vitamin D supplementation (100,000-U bolus intramuscularly plus 50,000 U orally weekly) in addition to asthma controllers.

RESULTS:

FEV1 improved significantly in both groups after 8 weeks, but no significant difference was found between the 2 groups at baseline (P = .20) or after 8 weeks (P = .99); however, a significant improvement was seen in the intervention group in the last 16 weeks, and FEV1 was significantly better in the intervention group than the other group after 24 weeks (P < .001).

CONCLUSION:

Vitamin D supplementation associated with asthma controllers could significantly improve FEV1 in mild to moderate persistent asthma after 24 weeks.

Community paediatrics and social support

(see also Environmental health)

Glob Health Action. 2014 Aug 25;7:25310. doi: 10.3402/gha.v7.25310. eCollection 2014.

Child Support Grant access and receipt among 12-week-old infants in an urban township setting in South Africa.

Zembe-Mkabile W[1], Doherty T[2], Sanders D[3], Jackson D[4].

Health Systems Research Unit, South African Medical Research Council, Cape Town, South Africa; School of Public Health, University of the Western Cape, Cape Town, South Africa; Knowledge Management & Implementation Research Unit Health Section, UNICEF, New York, USA.

BACKGROUND:

Cash transfers (CTs) are increasingly used as a strategy to alleviate poverty and improve child health outcomes in low- and middle-income countries. The Child Support Grant (CSG) is the largest CT programme in South Africa, and on the continent, targeting poor children from birth until the age of 18 with a monthly sum of R300 (USD30). Evidence on the CSG shows that early receipt of the grant is associated with improved child health outcomes. Since its implementation, one of the major concerns about the grant has been take-up rates, particularly for younger children. This paper reports results on take-up rates for 12-week-old infants residing in an urban township in South Africa.

METHODS:

This is a descriptive study utilising data from a community-based, cluster-randomised trial which evaluated a programme providing pregnancy and post-natal home visits by community health workers to 3,494 mothers in Umlazi township, South Africa.

RESULTS:

At the 12-week visit, half (52%) of the mothers who had enrolled in the study had applied for the CSG on behalf of their children, while 85% of the mothers who had not applied were still planning to apply. Only 38% (1,327) of all children had received the CSG.

CONCLUSIONS:

In this study, many mothers had not applied for the CSG in the first few months after delivery, and only a third of children had accessed the grant. Further research is needed to understand what the current barriers are that prevent mothers from applying for this important form of social protection in the early months after delivery.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4145105/pdf/GHA-7-25310.pdf

Trials. 2014 Jul 23;15:298. doi: 10.1186/1745-6215-15-298.

Feasibility and pilot study of the effects of microfinance on mortality and nutrition in children under five amongst the very poor in India: study protocol for a cluster randomized controlled trial.

Ojha S, Szatkowski L, Sinha R, Yaron G, Fogarty A, Allen S, Choudhary S, Smyth AR[1].

Division of Child Health, Obstetrics and Gynaecology, University of Nottingham, Queen's Medical Center, Derby Road, NG7 2UH Nottingham, UK. Alan.smyth@nottingham.ac.uk

BACKGROUND:

The United Nations Millennium Development Goals include targets for the health of children under five years old. Poor health is linked to poverty and microfinance initiatives are economic interventions that may improve health by breaking the cycle of poverty. However, there is a lack of reliable evidence to support this. In addition, microfinance schemes may have adverse effects on health, for example due to increased indebtedness. Rojiroti UK and the Centre for Promoting Sustainable Livelihood run an innovative microfinance scheme that provides microcredit via women's self-help groups (SHGs). This pilot study, conducted in rural Bihar (India), will establish whether it is feasible to collect anthropometric and mortality data on children under five years old and to conduct a limited cluster randomized trial of the Rojiroti intervention.

METHODS/DESIGN:

We have designed a cluster randomized trial in which participating tolas (small communities within villages) will be randomized to either receive early (SHGs and microfinance at baseline) or late intervention (SHGs and microfinance after 18 months). Using predesigned questionnaires, demographic, and mortality data for the last year and information about participating mothers and their children will be collected and the weight, height, and mid upper arm circumference (MUAC) of children will be measured at baseline and at 18 months. The late intervention group will establish SHGs and microfinance support at this point and data collection will be repeated at 36 months.The primary outcome measure will be the mean weight for height z-score of children under five years old in the early and late intervention tolas at 18 months. Secondary outcome measures will be the mortality rate, mean weight for age, height for age, prevalence of underweight, stunting, and wasting among children under five years of age.

DISCUSSION:

Despite economic progress, marked inequalities in child health persist in India and Bihar is one of the worst affected states. There is a need to evaluate programs that may alleviate poverty and improve health. This study will help to inform the design of a definitive trial to determine if the Rojiroti scheme can improve the nutrition and survival of children under five years of age in deprived rural communities.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4119203/pdf/13063_2014_Article_2171.pdf

J Nutr. 2014 Oct;144(10):1627-36. doi: 10.3945/jn.114.194464. Epub 2014 Aug 20.

Program impact pathway analysis of a social franchise model shows potential to improve infant and young child feeding practices in Vietnam.

Nguyen PH[1], Menon P[2], Keithly SC[3], Kim SS[4], Hajeebhoy N[5], Tran LM[5], Ruel MT[4], Rawat R[4].

International Food Policy Research Institute (IFPRI), Hanoi, Vietnam, Institute of Social and Medical Studies, Hanoi, Vietnam

Abstract

By mapping the mechanisms through which interventions are expected to achieve impact, program impact pathway (PIP) analysis lays out the theoretical causal links between program activities, outcomes, and impacts. This study examines the pathways through which the Alive & Thrive (A&T) social franchise model is intended to improve infant and young child feeding (IYCF) practices in Vietnam. Mixed methods were used, including qualitative interviews with franchise management board members (n = 12), surveys with health providers (n = 120), counseling observations (n = 160), and household surveys (n = 2045). Six PIP components were assessed: 1) franchise management, 2) training and IYCF knowledge of health providers, 3) service delivery, 4) program exposure and utilization, 5) maternal behavioral determinants (knowledge, beliefs, and intentions) toward optimal IYCF practices, and 6) IYCF practices. Data were collected from A&T-intensive areas (A&T-I; mass media + social franchise) and A&T-nonintensive areas (A&T-NI; mass media only) by using a cluster-randomized controlled trial design. Data from 2013 were compared with baseline where similar measures were available. Results indicate that mechanisms are in place for effective management of the franchise system, despite challenges to routine monitoring. A&T training was associated with increased capacity of providers, resulting in higher-quality IYCF counseling (greater technical knowledge and communication skills during counseling) in A&T-I areas. Franchise utilization increased from 10% in 2012 to 45% in 2013 but fell below the expected frequency of 9-15 contacts per mother-child dyad. Improvements in breastfeeding knowledge, beliefs, intentions, and practices were greater among mothers in A&T-I areas than among those in A&T-NI areas. In conclusion, there are many positive changes along the impact pathway of the franchise services, but challenges in utilization and demand creation should be addressed to achieve the full intended impact.

Dengue

(see Vaccines - dengue)

Cochrane Database Syst Rev. 2014 Jul 1;7:CD003488. doi: 10.1002/14651858.CD003488.pub3.

Corticosteroids for dengue infection.

Zhang F[1], Kramer CV.

School of Public Health and Management, Chongqing Medical University, No. 1, Yi Xue Yuan Road, Chongqing, China, 400016.

BACKGROUND:

Dengue is a common and important mosquito-borne viral infection. In many low- and middle-income countries it is endemic and is an important public health problem. Severe dengue is an important cause of death in children. There is no specific treatment for dengue, but observational studies suggest corticosteroids may have a benefit in dengue-related shock, and some people believe corticosteroids may prevent the progression to severe illness if given early in the course of the illness.

OBJECTIVES:

To compare treatment of dengue with and without use of corticosteroids or placebo in relation to preventing shock-related death and disease progression in children and adults.

SEARCH METHODS:

We searched the Cochrane Infectious Disease Group Centralized Register; CENTRAL; MEDLINE; EMBASE; and LILACS, up to 6 January 2014. We screened reference lists and contacted the relevant study authors for additional information where required.

SELECTION CRITERIA:

Randomized controlled trials or quasi-randomized controlled trials comparing corticosteroids with placebo or no corticosteroids in patients diagnosed with dengue-related shock, or patients in an early symptomatic state of dengue with positive serology.

DATA COLLECTION AND ANALYSIS:

Two researchers independently screened eligibility of records, extracted data and assessed quality of the studies. We presented findings in meta-analysis and summary of findings tables and evaluated the quality of evidence using GRADE.

MAIN RESULTS:

We included eight studies enrolling 948 participants in this review. Paitents with dengue-related shock Four studies enrolled children younger than 15 years with dengue-related shock at hospitals in Southeast Asia and evaluated intravenous corticosteroids. The trials did not detect an effect on death (four trials, 284 participants, very low quality evidence), the need for blood transfusion (two trials, 89 participants, very low quality evidence), pulmonary haemorrhage (one trial, 63 participants, very low quality evidence), convulsions (one trial, 63 participants, very low quality evidence), or duration of hospitalization (one trial, 63 participants, very low quality evidence). The body of evidence is too small to confidently prove or exclude clinically important effects. Furthermore, the trials are more than 20 years old with several methodological limitations. Patients with dengue at an early stage Four studies enrolled 664 children and adults with dengue at an early stage of infection (without shock) in Columbia, India, Sri Lanka and Vietnam. In these participants there were no evidence of effects of oral or intravenous corticosteroids on mortality (four trials, 664 participants, low quality evidence), or on the development of complications of severe dengue such as shock (two trials, 286 participants, very

low quality evidence), severe bleeding (two trials, 425 participants, very low quality evidence), severe thrombocytopaenia (one trial, 225 participants, very low quality evidence), ascites (one trial, 178 participants, very low quality evidence) and intensive care unit (ICU) admissions (two trials, 286 participants, very low quality evidence).

AUTHORS' CONCLUSIONS:

The evidence from trials using corticosteroids in dengue is inconclusive and the quality of evidence is low to very low. This applies to both the use of corticosteroids in dengue-related shock and for dengue at an early stage. There is insufficient evidence to evaluate the effects of corticosteroids in the treatment of early stage dengue fever and dengue-related shock outside of the context of a randomized controlled trial.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003488.pub3/pdf

Glob Health Action. 2014 Sep 1;7:24887. doi: 10.3402/gha.v7.24887. eCollection 2014.

Acceptability of impregnated school uniforms for dengue control in Thailand: a mixed methods approach.

Murray N[1], Jansarikij S[2], Olanratmanee P[2], Maskhao P[3], Souares A[1], Wilder-Smith A[4], Kittayapong P[2], Louis VR[5].

Institute of Public Health, University of Heidelberg, Heidelberg, Germany; Center of Excellence for Vectors and Vector-Borne Diseases, Faculty of Science, Mahidol University, Salaya, Nakhon Pathom, Thailand; Faculty of Humanities and Social Sciences, Rajabhat Rajanagarindra University, Chachoengsao, Thailand.

BACKGROUND:

As current dengue control strategies have been shown to be largely ineffective in reducing dengue in school-aged children, novel approaches towards dengue control need to be studied. Insecticide-impregnated school uniforms represent an innovative approach with the theoretical potential to reduce dengue infections in school children.

OBJECTIVES:

This study took place in the context of a randomised control trial (RCT) to test the effectiveness of permethrin-impregnated school uniforms (ISUs) for dengue prevention in Chachoengsao Province, Thailand. The objective was to assess the acceptability of ISUs among parents, teachers, and principals of school children involved in the trial.

METHODOLOGY:

Quantitative and qualitative tools were used in a mixed methods approach. Class-clustered randomised samples of school children enrolled in the RCT were selected and their parents completed 321 self-administered questionnaires. Descriptive statistics and logistic regression were used to analyse the quantitative data. Focus group discussions and individual semi-structured interviews were conducted with parents, teachers, and principals. Qualitative data analysis involved content analysis with coding and thematic development.

RESULTS:

The knowledge and experience of dengue was substantial. The acceptability of ISUs was high. Parents (87.3%; 95% CI 82.9-90.8) would allow their child to wear an ISU and 59.9% (95% CI

53.7-65.9) of parents would incur additional costs for an ISU over a normal uniform. This was significantly associated with the total monthly income of a household and the educational level of the respondent. Parents (62.5%; 95% CI 56.6-68.1) indicated they would be willing to recommend ISUs to other parents.

CONCLUSIONS:

Acceptability of the novel tool of ISUs was high as defined by the lack of concern along with the willingness to pay and recommend. Considering issues of effectiveness and scalability, assessing acceptability of ISUs over time is recommended.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4152550/pdf/GHA-7-24887.pdf

Development, cerebral palsy and mental health

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

Pediatrics. 2014 Oct;134(4):e1001-8. doi: 10.1542/peds.2014-0694.

Cognitive deficit and poverty in the first 5 years of childhood in Bangladesh.

Hamadani JD[1], Tofail F[2], Huda SN[3], Alam DS[2], Ridout DA[4], Attanasio O[5], Grantham-McGregor SM[6].

International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh; Institute of Nutrition and Food Science, Dhaka University, Dhaka, Bangladesh; Centre for Paediatric Epidemiology and Biostatistics, and Department of Economics, University College London, London, United Kingdom; Centre for International Health and Development, Institute of Child Health.

OBJECTIVE:

We aimed to determine the timing and size of the cognitive deficit associated with poverty in the first 5 years of life and to examine the role of parental characteristics, pre- and postnatal growth, and stimulation in the home in Bangladeshi children. We hypothesized that the effect of poverty on cognition begins in infancy and is mainly mediated by these factors.

METHODS:

We enrolled 2853 singletons, a subsample from a pregnancy supplementation trial in a poor rural area. We assessed mental development at 7, 18, and 64 months; anthropometry at birth, 12, 24, and 64 months; home stimulation at 18 and 64 months; and family's socioeconomic background. In multiple regression analyses, we examined the effect of poverty at birth on IQ at 64 months and the extent that other factors mediated the effect.

RESULTS:

A mean cognitive deficit of 0.2 (95% confidence interval -0.4 to -0.02) z scores between the first and fifth wealth quintiles was apparent at 7 months and increased to 1.2 (95% confidence interval -1.3 to -1.0) z scores of IQ by 64 months. Parental education, pre- and postnatal growth in length, and home stimulation mediated 86% of the effects of poverty on IQ and had independent effects. Growth in the first 2 years had larger effects than later growth. Home stimulation had effects throughout the period.

CONCLUSIONS:

Effects of poverty on children's cognition are mostly mediated through parental education, birth size, growth in the first 24 months, and home stimulation in the first 5 years.

http://pediatrics.aappublications.org/content/134/4/e1001.full

Lancet. 2014 Oct 4;384(9950):1282-93. doi: 10.1016/S0140-6736(14)60455-4. Epub 2014 Jun 16.

Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial.

Yousafzai AK[1], Rasheed MA[2], Rizvi A[2], Armstrong R[3], Bhutta ZA[4].

Department of Paediatrics and Child Health, Division of Women and Child Health, Aga Khan University, Karachi, Pakistan; Aga Khan University-East Africa, Nairobi, Kenya; Department of Paediatrics and Child Health, Division of Women and Child Health, Aga Khan University, Karachi, Pakistan; Center for Global Child Health, Hospital for Sick Children, Toronto, ON, Canada.

BACKGROUND:

Stimulation and nutrition delivered through health programmes at a large scale could potentially benefit more than 200 million young children worldwide who are not meeting their developmental potential. We investigated the feasibility and effectiveness of the integration of interventions to enhance child development and growth outcomes in the Lady Health Worker (LHW) programme in Sindh, Pakistan.

METHODS:

We implemented a community-based cluster-randomised effectiveness trial through the LHW programme in rural Sindh, Pakistan, with a 2 × 2 factorial design. We randomly allocated 80 clusters (LHW catchments) of children to receive routine health and nutrition services (controls; n=368), nutrition education and multiple micronutrient powders (enhanced nutrition; n=364), responsive stimulation (responsive stimulation; n=383), or a combination of both enriched interventions (n=374). The allocation ratio was 1:20 (ie, 20 clusters per intervention group). The data collection team were masked to the allocated intervention. All children born in the study area between April, 2009, and March, 2010, were eligible for enrolment if they were up to 2·5 months old without signs of severe impairments. Interventions were delivered by LHWs to families with children up to 24 months of age in routine monthly group sessions and home visits. The primary endpoints were child development at 12 and 24 months of age (assessed with the Bayley Scales of Infant and Toddler Development, Third Edition) and growth at 24 months of age. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT007159636.

FINDINGS:

1489 mother-infant dyads were enrolled into the study, of whom 1411 (93%) were followed up until the children were 24 months old. Children who received responsive stimulation had significantly higher development scores on the cognitive, language, and motor scales at 12 and 24 months of age, and on the social-emotional scale at 12 months of age, than did those who did

not receive the intervention. Children who received enhanced nutrition had significantly higher development scores on the cognitive, language, and social-emotional scales at 12 months of age than those who did not receive this intervention, but at 24 months of age only the language scores remained significantly higher. We did not record any additive benefits when responsive stimulation was combined with nutrition interventions. Responsive stimulation effect sizes (Cohen's d) were 0·6 for cognition, 0·7 for language, and 0·5 for motor development at 24 months of age; these effect sizes were slightly smaller for the combined intervention group and were low to moderate for the enhanced nutrition intervention alone. Children exposed to enhanced nutrition had significantly better height-for-age Z scores at 6 months ($p<0·0001$) and 18 months ($p=0·02$) than did children not exposed to enhanced nutrition. Longitudinal analysis showed a small benefit to linear growth from enrolment to 24 months ($p=0·026$) in the children who received the enhanced nutrition intervention.

INTERPRETATION:

The responsive stimulation intervention can be delivered effectively by LHWs and positively affects development outcomes. The absence of a major effect of the enhanced nutrition intervention on growth shows the need for further analysis of mediating variables (eg, household food security status) that will help to optimise future nutrition implementation design.

http://pediatrics.aappublications.org/content/134/4/e1001.full

BMJ. 2014 Sep 29;349:g5785. doi: 10.1136/bmj.g5785.

Using the infrastructure of a conditional cash transfer program to deliver a scalable integrated early child development program in Colombia: cluster randomized controlled trial.

Attanasio OP[1], Fernández C[2], Fitzsimons EO[3], Grantham-McGregor SM[4], Meghir C[5], Rubio-Codina M[6].

Department of Economics, University College London, London, UK; Mathematica Policy Research, Princeton, NJ, USA; Institute of Education, London WC1H 0AL, UK; UCL Institute of Child Health, London, UK; Department of Economics, Yale University, New Haven, CT, USA; Centre for the evaluation of development policy, Institute for Fiscal Studies, London.

OBJECTIVE:

To assess the effectiveness of an integrated early child development intervention, combining stimulation and micronutrient supplementation and delivered on a large scale in Colombia, for children's development, growth, and hemoglobin levels.

DESIGN:

Cluster randomized controlled trial, using a 2 × 2 factorial design, with municipalities assigned to one of four groups: psychosocial stimulation, micronutrient supplementation, combined intervention, or control.

SETTING:

96 municipalities in Colombia, located across eight of its 32 departments.

PARTICIPANTS:

1420 children aged 12-24 months and their primary carers.

INTERVENTION:

Psychosocial stimulation (weekly home visits with play demonstrations), micronutrient sprinkles given daily, and both combined. All delivered by female community leaders for 18 months.

MAIN OUTCOME MEASURES:

Cognitive, receptive and expressive language, and fine and gross motor scores on the Bayley scales of infant development-III; height, weight, and hemoglobin levels measured at the baseline and end of intervention.

RESULTS:

Stimulation improved cognitive scores (adjusted for age, sex, testers, and baseline levels of outcomes) by 0.26 of a standard deviation (P=0.002). Stimulation also increased receptive language by 0.22 of a standard deviation (P=0.032). Micronutrient supplementation had no significant effect on any outcome and there was no interaction between the interventions. No intervention affected height, weight, or hemoglobin levels.

CONCLUSIONS:

Using the infrastructure of a national welfare program we implemented the integrated early child development intervention on a large scale and showed its potential for improving children's cognitive development. We found no effect of supplementation on developmental or health outcomes. Moreover, supplementation did not interact with stimulation. The implementation model for delivering stimulation suggests that it may serve as a promising blueprint for future policy on early childhood development.Trial registration Current Controlled trials ISRCTN18991160.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4179481/pdf/bmj.g5785.pdf

J Child Psychol Psychiatry. 2014 Nov;55(11):1251-9. doi: 10.1111/jcpp.12247. Epub 2014 May 9.

Development of children at risk for adverse outcomes participating in early intervention in developing countries: a randomized controlled trial.

Wallander JL[1], Bann CM, Biasini FJ, Goudar SS, Pasha O, Chomba E, McClure E, Carlo WA.

University of California, Merced, CA, USA.

BACKGROUND:

Previous research has indicated positive effects of early developmental intervention (EDI) on the development of children in developing countries. Few studies, however, have examined longitudinally when differential treatment effects may be observed and whether differential outcomes are associated with exposure to different risk factors and country of implementation. Also, birth asphyxia as a risk condition has not been well studied. To address these limitations, we conducted a randomized controlled trial to test the hypothesis that there will be differential developmental trajectories favoring those who receive EDI versus a health education intervention in children in rural areas of India, Pakistan, and Zambia.

METHODS:

Children with and without birth asphyxia were randomized to EDI or control intervention, which was implemented by parents who received training in biweekly home visits initiated before child age 1 month and continuing until 36 months. Development was assessed in 376 children at ages 12, 24, and 36 months using the Bayley Scales of Infant Development and Ages & Stages Questionnaire administered by evaluators blind to intervention assignment and risk condition.

RESULTS:

Longitudinal mixed model analysis indicated that EDI resulted in better development over 36 months in cognitive abilities, regardless of risk condition, maternal resources, child gender, or country. Psychomotor development and parent-reported general development showed similar trends as for cognitive abilities, but were not statistically different between intervention conditions. Developmental differences were observed first at 36 months of age.

CONCLUSION:

Early developmental intervention has promise for improving development in children across developing countries when exposed to various risk conditions. EDI should be one prominent approach used to begin to address long-term outcomes and intergenerational transmission of poverty.

Comment
How can there be no person representing an institution in India, Pakistan or Zambia involved in this study to the extent that they deserved authorship?

Indian Pediatr. 2014 Jul;51(7):550-4.

Comparative short term efficacy and tolerability of methylphenidate and atomoxetine in attention deficit hyperactivity disorder.

Garg J[1], Arun P, Chavan BS.

Department of Psychiatry, Government Medical College and Hospital, Chandigarh, India. Correspondence to: Dr Jasmin Garg, Department of Psychiatry, Government Medical College and Hospital, Sector 32, Chandigarh, India. jasmin.arneja@gmail.com

OBJECTIVE:

To compare the short term efficacy and tolerability of methylphenidate and atomoxetine in children with Attention deficit hyperactivity disorder (ADHD).

DESIGN:

Open label randomized parallel group clinical trial.

SETTING:

Child Guidance Clinic of a tertiary care hospital of Northern India from October 2010 to June 2012.

PARTICIPANTS:

69 patients (age 6-14 y) with a diagnosis of ADHD receiving methylphenidate or atomoxetine.

INTERVENTION:

Methylphenidate (0.2-1 mg/kg/d) or atomoxetine (0.5-1.2 mg/kg/d) for eight weeks.

MAIN OUTCOME MEASURES:

Treatment response (>25% change in baseline Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS); Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADTRS); Clinical Global Impression Severity Scale (CGI-S) at eight weeks and adverse effects.

RESULTS:

Treatment response was observed in 90.7% patients from methylphenidate group and 86.2% patients of atomoxetine group at an average dose of 0.45 mg/kg/d and 0.61 mg/kg/d, respectively. The patients showed comparable improvement on VADPRS (P=0.500), VADTRS (P=0.264) and CGI-S (P=0.997). Weight loss was significantly higher in methylphenidate group (-0.57±0.78 kg; P=0.001), and heart rate increase was observed at higher rate in atomoxetine group (7± 9 bpm; P=0.021).

CONCLUSIONS:

Methylphenidate and atomoxetine are efficacious in Indian children with ADHD at lesser doses than previously used. Their efficacy and tolerability are comparable

http://www.indianpediatrics.net/july2014/550.pdf

Clin Rehabil. 2014 Oct;28(10):1004-14. doi: 10.1177/0269215514533710. Epub 2014 May 16.

The clinical impact of orthotic correction of lower limb rotational deformities in children with cerebral palsy: a randomized controlled trial.

Abd El-Kafy EM[1].

Department of Physical Therapy for Disturbances of Growth and Developmental Disorders in Children and its Surgery, Faculty of Physical Therapy, Cairo University, Giza, EgyptDepartment of Physical Therapy, Faculty of Applied Medical Sciences, Umm Al Qura University, Makkah, Saudi Arabia ehabkafy@yahoo.com

OBJECTIVE:

This study aimed to evaluate the effectiveness of a static ground reaction ankle foot orthosis and strapping system on improving gait parameters in children with spastic diplegic cerebral palsy.

SETTING:

The current study was conducted at the physical therapy faculty of Cairo University, Egypt.

SUBJECTS:

This study included 57 children of both sexes, aged 6 to 8 years.

STUDY DESIGN:

Three-armed randomized control trial.

INTERVENTION:

Participants in all groups received a traditional neuro-developmental physical therapy program that included standing and gait training exercises. Children in group A performed the training program without any orthotic management, in group B with the TheraTogs strapping system, and in group C with the TheraTogs strapping system and static ground reaction ankle foot orthoses. Children underwent treatment for two hours daily, except on weekends, for twelve successive weeks.

MAIN MEASURE:

Gait speed, cadence, stride length, and hip and knee flexion angles in the mid-stance phase were evaluated pre-and post-treatment using a three-dimensional motion analysis system (pre-reflex system).

RESULTS:

Statistically significant differences were recorded among the three groups post-treatment in gait speed, cadences, and stride length. The P-values for these variable differences were 0.03, 0.011, and 0.001 respectively. Significant post-treatment differences were also recorded for bilateral hip-and knee-flexion angles. For all measured parameters, better significant results were registered for group C than for the other groups.

CONCLUSION:

Orthotic intervention composed of a static ground reaction ankle foot orthosis combined with the TheraTogs strapping system improves gait more than conventional treatment with or without TheraTogs in children with spastic diplegic cerebral palsy.

J Child Psychol Psychiatry. 2014 Nov 17. doi: 10.1111/jcpp.12352. [Epub ahead of print]

The impact of dialogic book-sharing training on infant language and attention: a randomized controlled trial in a deprived South African community.

Vally Z[1], Murray L, Tomlinson M, Cooper PJ.

School of Psychology and Clinical Language Sciences, Winnicott Research Unit, University of Reading, Reading, UK.

BACKGROUND:

Dialogic book-sharing is an interactive form of shared reading. It has been shown in high income countries (HICs) to be of significant benefit to child cognitive development. Evidence for such benefit in low and middle income countries (LMICs) is scarce, although a feasibility study of our own produced encouraging findings. Accordingly, we aimed to establish the impact on child language and attention of providing training in dialogic booksharing to carers of infants in an impoverished South African community.

METHODS:

We conducted a randomized controlled trial in Khayelitsha, an informal settlement in South Africa. Mothers of infants aged between 14 and 16 months were recruited and randomized to either 8 weeks of manualized training in dialogic book-sharing or a no-intervention control group. Independent assessments were made of infant language and attention at baseline and following training. The trial was registered (ISRCTN39953901).

RESULTS:

Ninety one carer-infant dyads were recruited and randomized to the intervention group (n = 49) or the control group (n = 42), 82 (90%) of whom were available for follow-up assessments. On a standardized carer report of infant vocabulary, compared to those in the control group, carers who received the intervention reported a significantly greater increase in the number of words understood by their infants as well as a larger increase in the number of words that their infant understood and could vocalize. Intervention group children also showed substantially greater gains on a measure of sustained attention.

CONCLUSIONS:

In line with evidence from HICs, a dialogic book-sharing programme delivered to an impoverished South African sample was shown to be of considerable benefit to the development of child language and focussed attention. The training programme, which is simple and inexpensive to deliver, has the potential to benefit child cognitive development in LMIC contexts where such development is commonly compromised.

Infant Behav Dev. 2014 Nov;37(4):556-61. doi: 10.1016/j.infbeh.2014.06.011. Epub 2014 Jul 24.

Prenatal meditation influences infant behaviors.

Chan KP[1].

The Buddhist Institute of Enlightenment (Hk) Ltd., 270 Sha Tsui Road 2/F, Tsuen Wan, Hong Kong. Electronic address: drchankapo@gmail.com

Abstract

Meditation is important in facilitating health. Pregnancy health has been shown to have significant consequences for infant behaviors. In view of limited studies on meditation and infant temperament, this study aims to explore the effects of prenatal meditation on these aspects. The conceptual framework was based on the postulation of positive relationships between prenatal meditation and infant health. A randomized control quantitative study was carried out at Obstetric Unit, Queen Elizabeth Hospital in Hong Kong. 64 pregnant Chinese women were recruited for intervention and 59 were for control. Outcome measures were cord blood cortisol, infant salivary cortisol, and Carey Infant Temperament Questionnaire. Cord blood cortisol level of babies was higher in the intervention group ($p<0.01$) indicates positive health status of the newborns verifies that prenatal meditation can influence fetal health. Carey Infant Temperament Questionnaire showed that the infants of intervention group have better temperament ($p<0.05$) at fifth month reflects the importance of prenatal meditation in relation to child health. Present study concludes the positive effects of prenatal meditation on infant behaviors and recommends that pregnancy care providers should provide prenatal meditation to pregnant women.

Diarrhoea

(See also: Vaccines and immunization - Rotavirus vaccine, Hygiene and Environmental health)

J Pediatr Gastroenterol Nutr. 2014 Aug;59(2):167-71. doi: 10.1097/MPG.0000000000000398.

Bovine complex milk lipid containing gangliosides for prevention of rotavirus infection and diarrhoea in northern Indian infants.

Poppitt SD[1], McGregor RA, Wiessing KR, Goyal VK, Chitkara AJ, Gupta S, Palmano K, Kuhn-Sherlock B, McConnell MA.

Human Nutrition Unit, School of Biological Sciences, University of Auckland, New Zealand †Panchsheel Hospital, Yamuna Vihar ‡Sarvodaya Child Care, Pitampura, New Delhi §M.V. Hospital & Research Centre, Lucknow, India ||Research and Development Centre, Palmerston North ¶University of Otago, Dunedin, New Zealand.

Abstract

Rotavirus (RV) is a leading cause of morbidity and mortality in children younger than 5 years of age, presenting commonly with diarrhoeal symptoms. In a prospective 12-week double-blind randomised controlled trial we assessed acceptability and efficacy of a high-ganglioside complex milk lipid (CML) for prevention of RV infection in 450 infants, ages 8 to 24 months, at 3 sites in northern India. Prevalence of diarrhoea and RV was unseasonably low at baseline (all-cause diarrhoea [ACD], n=16; RV diarrhoea [RVD], n=2; RV infection, RV positive [RV+], n=20) and throughout the trial, with only 110 total episodes of ACD for 12 weeks (CML, n=62; control, n=48) of which 10 were RVD (CML, n=4; control, n=6). Mean duration that RVD persisted was lower in the CML group (2.3±0.5 days) than that in the control group (3.8±1.3 days, P=0.03), but only 3 of 450 end of trial stool samples were identified as RV+ (<1%; CML, n=2; control, n=1). This hampered the assessment of efficacy of CML, despite the large a priori determined sample size. During the trial similar numbers of infants reported adverse events (AEs: CML 41%, control 46%), with the majority of events classified as mild and not related to the intervention. In conclusion, further clinical trials against a higher background of seasonal prevalence are necessary to assess efficacy of this nutritional intervention to prevent RVD. More important, however, high-ganglioside CML was acceptable for long-term consumption in infants ages 8 to 24 months.

Clin Gastroenterol Hepatol. 2014 Sep;12(9):1507-13.e1. doi: 10.1016/j.cgh.2014.01.024. Epub 2014 Jan 22.

Zinc or albendazole attenuates the progression of environmental enteropathy: a randomized controlled trial.

Ryan KN[1], Stephenson KB[1], Trehan I[2], Shulman RJ[3], Thakwalakwa C[4], Murray E[1], Maleta K[4], Manary MJ[5].

Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri; Department of Paediatrics and Child Health, University of Malawi College of Medicine, Blantyre, Malawi; Children's Nutrition Research Center, Baylor College of Medicine, Houston, Texas; Department of Community Health, University of Malawi College of Medicine, Blantyre, Malawi, manary@kids.wustl.edu

BACKGROUND & AIMS:

Environmental enteropathy (EE) is a subclinical condition among children in the developing world, characterized by T-cell infiltration of the small-bowel mucosa and diffuse villous atrophy. EE leads to macronutrient and micronutrient malabsorption and stunting, with a resultant increased risk for infection and reduced cognitive development. We tested the hypothesis that zinc and albendazole treatments would reduce the severity of EE in rural African children.

METHODS:

In a randomized, double-blind, placebo-controlled trial in rural southern Malawi, asymptomatic children, 1 to 3 years old and at high risk for EE, received either a single dose of albendazole, a 14-day course of 20 mg zinc sulfate, or a placebo. Subjects were given the dual-sugar absorption test, and the ratio of lactulose to mannitol (L:M) in urine was used to determine the severity of EE at baseline and 34 days after completion of the assigned regimen. The primary outcome was the change in the L:M.

RESULTS:

A complete set of urine samples was obtained from 222 of 234 children enrolled and analyzed. The mean baseline L:M was 0.32 ± 0.18 among all children and did not differ among groups (normal L:M range, <0.12). At the end of the study, the L:M ratio had increased more in the placebo group (0.12 ± 0.31) than in the zinc group (0.03 ± 0.20; $P < .03$) or the albendazole group (0.04 ± 0.22; $P < .04$).

CONCLUSIONS:

Treatment with zinc or albendazole protects against a significant increase in the L:M ratio, a biomarker for EE, in asymptomatic rural Malawian children. These findings could provide insight into the etiology and pathogenesis of EE.

Trials. 2015 Feb 8;16:46. doi: 10.1186/s13063-015-0565-9.

Lactose-free milk for infants with acute gastroenteritis in a developing country: study protocol for a randomized controlled trial.

Nabulsi M, Yazbeck N, Charafeddine F.

BACKGROUND:

Acute gastroenteritis is a major cause of pediatric morbidity and mortality, accounting for 15% of all childhood deaths worldwide. In developing countries, diarrheal diseases continue to be a major public health burden. Evidence from developed countries suggests that intake of lactose-free milk during diarrheal episodes may reduce the duration of the illness in pediatric inpatients. It is unknown whether lactose-free milk reduces the severity or duration of acute gastroenteritis in infants treated in outpatient settings in developing countries where diarrhea is more severe, and results in higher morbidities and mortalities. We hypothesize that lactose-free milk intake during acute gastroenteritis would significantly decrease the duration and severity of diarrhea in infants presenting to the Emergency Department (ED), as compared with lactose-containing milk.

METHODS/DESIGN:

An open-label randomized clinical trial.

STUDY POPULATION:

40 infants with acute gastroenteritis, age between 2 and 12 months, presenting to the ED, will be randomized to control or intervention group.

INTERVENTION:

Lactose-free milk, whereas the control group will continue on regular infant formula for a total of 7 days. Infants will be followed up for 7 days.

OUTCOME MEASURES:

Diarrhea duration, weight loss, illness clinic visits, hospitalization rate, parental satisfaction, and time to symptom resolution.

STATISTICAL ANALYSIS:

Descriptive and regression analysis will be conducted under the intention-to-treat basis by using SPSS version 21.

DISCUSSION:

Acute gastroenteritis is a public health burden for developing countries, with a significant impact on infant morbidity and mortality. Provision of infant formula that may reduce the duration and severity of diarrhea can decrease this burden in countries with limited healthcare resources, like Lebanon. The findings from this study are anticipated to provide evidence-based dietary recommendations for ambulatory infants with acute diarrhea in developing countries.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4324790/

Comment
The implications of this study should be carefully considered before it is conducted. Although it plans to enrol only babies over 2 months who are not breast-fed, the results may be seized on by formula companies and lactose-free milk marketed as a treatment for diarrhoea in developing countries.

Water purification

Am J Trop Med Hyg. 2014 Jul;91(1):190-7. doi: 10.4269/ajtmh.13-0568. Epub 2014 May 27.

A cluster randomized controlled trial to reduce childhood diarrhea using hollow fiber water filter and/or hygiene-sanitation educational interventions.

Lindquist ED[1], George CM[2], Perin J[2], Neiswender de Calani KJ[2], Norman WR[2], Davis TP Jr[2], Perry H[2].

Department of Biological Sciences, School of Science, Engineering and Health, Messiah College, Mechanicsburg, Pennsylvania; Department of International Health, Program in Global Disease Epidemiology and Control, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Fundación contra el Hambre-Bolivia, Zona Sopocachi, La Paz, Bolivia;

School of Science, Engineering and Health, Messiah College, Mechanicsburg, Pennsylvania; Food for the Hungry-USA, Phoenix, Arizona; Department of International Health, Health Systems Program, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
quist@messiah.edu

Abstract

Safe domestic potable water supplies are urgently needed to reduce childhood diarrheal disease. In periurban neighborhoods in Cochabamba, Bolivia, we conducted a cluster randomized controlled trial to evaluate the efficacy of a household-level hollow fiber filter and/or behavior change communication (BCC) on water, sanitation, and hygiene (WASH) to reduce the diarrheal disease in children less than 5 years of age. In total, 952 households were followed for a period of 12 weeks post-distribution of the study interventions. Households using Sawyer PointONE filters had significantly less diarrheal disease compared with the control arm during the intervention period, which was shown by diarrheal prevalence ratios of 0.21 (95% confidence interval [95% CI] = 0.15-0.30) for the filter arm and 0.27 (95% CI = 0.22-0.34) for the filter and WASH BCC arm. A non-significant reduction in diarrhea prevalence was reported in the WASH BCC study arm households (0.71, 95% CI = 0.59-0.86).

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080561/

Endocrine disorders and bone health

JAMA Pediatr. 2014 Nov;168(11):999-1005. doi: 10.1001/jamapediatrics.2014.1211.

Low-dose vs standard-dose insulin in pediatric diabetic ketoacidosis: a randomized clinical trial.

Nallasamy K[1], Jayashree M[1], Singhi S[1], Bansal A[1].

Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

IMPORTANCE:

The standard recommended dose (0.1 U/kg per hour) of insulin in diabetic ketoacidosis (DKA) guidelines is not backed by strong clinical evidence. Physiologic dose-effect studies have found that even lower doses could adequately normalize ketonemia and acidosis. Lowering the insulin dose may be advantageous in the initial hours of therapy when a gradual decrease in glucose, electrolytes, and resultant osmolality is desired.

OBJECTIVE:

To compare the efficacy and safety of low-dose insulin against the standard dose in children with DKA.

DESIGN, SETTING, AND PARTICIPANTS:

This was a prospective, open-label randomized clinical trial conducted in the pediatric emergency department and intensive care unit of a tertiary care teaching hospital in northern India from November 1, 2011, through December 31, 2012. A total of 50 consecutive children 12 years or younger with a diagnosis of DKA were randomized to low-dose (n = 25) and standard-dose (n = 25) groups.

INTERVENTIONS:

Low-dose (0.05 U/kg per hour) vs standard-dose (0.1 U/kg per hour) insulin infusion.

MAIN OUTCOMES AND MEASURES:

The primary outcome was the rate of decrease in blood glucose until a level of 250 mg/dL or less is reached (to convert to millimoles per liter, multiply by 0.0555). The secondary outcomes included time to resolution of acidosis, episodes of treatment failures, and incidences of hypokalemia and hypoglycemia.

RESULTS:

The mean (SD) rate of blood glucose decrease until a level of 250 mg/dL or less is reached (45.1 [17.6] vs 52.2 [23.4] mg/dL/h) and the mean (SD) time taken to achieve this target (6.0 [3.3] vs 6.2 [2.2] hours) were similar in the low- and standard-dose groups, respectively. Mean (SD) length of time to achieve resolution of acidosis (low vs standard dose: 16.5 [7.2] vs 17.2 [7.7] hours; P = .73) and rate of resolution of acidosis were also similar in the groups. Hypokalemia was seen in 12 children (48%) receiving the standard dose vs 5 (20%) of those receiving the low dose (P = .07); the tendency was more pronounced in malnourished children (7 [88%] vs 2 [28%]). Five children (20%) and 1 child (4%) receiving standard- and low-dose infusion (P = .17), respectively, developed hypoglycemia. Treatment failure was rare and comparable. One child in the standard-dose group developed cerebral edema, and no deaths occurred during the study period.

CONCLUSIONS AND RELEVANCE:

Low dose is noninferior to standard dose with respect to rate of blood glucose decrease and resolution of acidosis. We advocate a superiority trial with a larger sample size before 0.05 U/kg per hour replaces 0.1 U/kg per hour in the practice recommendations.

J Clin Endocrinol Metab. 2014 Sep;99(9):3169-76. doi: 10.1210/jc.2014-1150. Epub 2014 Apr 24.

The effect of prepubertal calcium carbonate supplementation on skeletal development in Gambian boys-a 12-year follow-up study.

Ward KA[1], Cole TJ, Laskey MA, Ceesay M, Mendy MB, Sawo Y, Prentice A.

Nutrition and Bone Health, Medical Research Council Human Nutrition Research, Cambridge CB1 9NL, United Kingdom; Population, Policy and Practice Programme, University College London, Institute of Child Health, London, United Kingdom; and Calcium, Vitamin D, and Bone Health, Medical Research Council, Keneba, The Gambia.

CONTEXT:

Calcium intake during growth is essential for future bone health but varies widely between individuals and populations. The impact on bone of increasing calcium intake is unknown in a population where low calcium intake, stunting, and delayed puberty are common.

OBJECTIVE:

To determine the effect of prepubertal calcium supplementation on mean age at peak velocity for bone growth and mineral accrual.

DESIGN AND SETTING:

Prospective follow-up of boys in rural Gambia, West Africa, who had participated in a double-blind, randomized, placebo-controlled trial of calcium supplementation.

PARTICIPANTS:

Eighty boys, initially aged 8.0-11.9 years, were followed up for 12 years.

INTERVENTIONS:

Subjects received 1 year of calcium carbonate supplementation (1000 mg daily, 5 d/wk).

MAIN OUTCOME MEASURES:

Dual-energy x-ray absorptiometry measurements were carried out for whole body (WB), lumbar spine, and total hip bone mineral content, bone area (BA), and WB lean mass. Super imposition by translation and rotation models was made to assess bone growth.

RESULTS:

Age at peak velocity was consistently earlier in the calcium group compared to the placebo group, for WB bone mineral content (mean, -6.2 [SE, 3.1]; P = .05), WB BA (mean, -7.0 [SE, 3.2] mo; P = .03), lumbar spine and total hip BA. By young adulthood, supplementation did not change the amount of bone accrued (mineral or size) or the rate of bone growth.

CONCLUSIONS:

Twelve months of prepubertal calcium carbonate supplementation in boys with a low calcium diet advanced the adolescent growth spurt but had no lasting effect on bone mineral or bone size. There is a need for caution when applying international recommendations to different populations.

Arch Dis Child. 2014 Sep;99(9):807-11. doi: 10.1136/archdischild-2013-305275. Epub 2014 Apr 19.

Vitamin D treatment in calcium-deficiency rickets: a randomised controlled trial.

Thacher TD[1], Fischer PR[2], Pettifor JM[3].

Department of Family Medicine, Mayo Clinic, Rochester, Minnesota, USA; Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA; MRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa.

OBJECTIVE:

To determine whether children with calcium-deficiency rickets have a better response to treatment with vitamin D and calcium than with calcium alone.

DESIGN:

Randomised controlled trial.

SETTING:

Jos University Teaching Hospital, Jos, Nigeria.

POPULATION:

Nigerian children with active rickets treated with calcium carbonate as limestone (approximately 938 mg elemental calcium twice daily) were, in addition, randomised to receive either oral vitamin D2 50,000 IU (Ca+D, n=44) or placebo (Ca, n=28) monthly for 24 weeks.

MAIN OUTCOME MEASURE:

Achievement of a 10-point radiographic severity score ≤1.5 and serum alkaline phosphatase ≤350 U/L.

RESULTS:

The median (range) age of enrolled children was 46 (15-102) months, and baseline characteristics were similar in the two groups. Mean (±SD) 25-hydroxyvitamin D (25(OH)D) was 30.2±13.2 nmol/L at baseline, and 29 (43%) had values <30 nmol/L. Baseline alkaline phosphatase and radiographic scores were unrelated to vitamin D status. Of the 68 children (94% of original cohort) who completed 24 weeks of treatment, 29 (67%) in the Ca+D group and 11 (44%) in the Ca group achieved the primary outcome (p=0.06). Baseline 25(OH)D did not alter treatment group effects (p=0.99 for interaction). At the end of 24 weeks, 25(OH)D values were 55.4±17.0 nmol/L and 37.9±20.0 nmol/L in the Ca+D and Ca groups, respectively, (p<0.001). In the Ca+D and Ca groups, the final 25(OH)D concentration was greater in those who achieved the primary outcome (56.4±17.2 nmol/L) than in those who did not (37.7±18.5 nmol/L, p<0.001).

CONCLUSIONS:

In children with calcium-deficiency rickets, there is a trend for vitamin D to improve the response to treatment with calcium carbonate as limestone, independent of baseline 25(OH)D concentrations.

J Musculoskelet Neuronal Interact. 2014 Sep;14(3):276-85.

Osteogenic effects of a physical activity intervention in South African black children.

Meiring RM[1], Micklesfield LK, Avidon I, McVeigh JA.

Exercise Laboratory, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

OBJECTIVES:

To determine whether a weight-bearing physical activity intervention improves measures of bone density, size and strength in a pre- and early pubertal cohort of black South African children.

METHODS:

Twenty two school children (9.7±1.1 years) were cluster randomised into an exercise (EX; n=12) and control (CON; n=10) group. EX children performed a weight-bearing exercise program for 20 weeks. CON children continued their regular activities. Whole body DXA and tibial peripheral QCT scans were obtained. Urine was analysed for concentrations of cross-linked N-telopeptides of Type I collagen (NTX).

RESULTS:

Changes in 4% volumetric BMD, area and strength were greater in EX than CON. At the 38% site, change in bone area and density was greater in EX than CON. The greater change in periosteal circumference in the EX groups also resulted in a greater change in cortical thickness of the tibia compared to the CON group. NTX concentration was lower in the EX group than the CON group after the intervention.

CONCLUSIONS:

This study documents for the first time the beneficial response of trabecular and cortical bone of black children to a weight bearing exercise intervention.

http://www.ismni.org/jmni/pdf/57/04MEIRING.pdf

Bone. 2014 Aug;65:69-76. doi: 10.1016/j.bone.2014.05.007. Epub 2014 May 15.

Effects of milk salt supplementation on bone mineral gain in pubertal Chinese adolescents: a 2-year randomized, double-blind, controlled, dose-response trial.

Zhang ZQ[1], Ma XM[1], Huang ZW[2], Yang XG[2], Chen YM[3], Su YX[4].

Guangdong Provincial Key Laboratory of Food, Nutrition, and Health, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong 510080, People's Republic of China; Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China.

BACKGROUND/OBJECTIVE:

Adequate calcium intakes may enhance bone mineral accumulation during childhood. Little is known about the optimal calcium intake in Chinese adolescents. We examined the effects of three levels of calcium intake on bone mineral accretion in adolescents.

METHODS:

This was a 2-year randomized, double-blind, controlled trial. The subjects were randomly assigned to receive 40 g of milk powder containing 300 mg of calcium and 200 IU of vitamin D (Low-Ca group), or same milk powder additionally fortified with 300 mg of calcium (Mid-Ca group) or 600 mg of calcium (High-Ca group) for 2 years. The subjects' bone mineral density (BMD) and bone mineral content (BMC) at the total body, lumbar spine and left hip were determined by dual-energy X-ray absorptiometry at baseline and after the second year of treatment. Of the 111 girls and 109 boys (aged 12-14 years) enrolled, 91 girls and 91 boys completed the trial.

RESULTS:

The girls in the High-Ca group (1,110 mg/d) had 2.3%, 2.7% and 2.6% greater BMD accretion at the total hip, femoral neck and shaft ($P<0.05$) but not at total body less head and spine than those in the Low-Ca group (655 mg/d). A significant effect of higher calcium intake was also observed for percentage change of size-adjusted BMC at femur neck ($P=0.047$). Bonferroni tests indicated no significant differences in the percentage changes in BMD, BMC or size-adjusted BMC between the Mid- and Low-Ca groups and between the High- and Mid-Ca groups. Extra calcium had no observable additional effect in the boys ($P>0.05$).

CONCLUSION:

An intake of 1000 mg/d or more might be helpful in maximizing bone mineral accretion in the hip for girls. But further large studies are required to identify its long-term effects and the optimal calcium intake for boys.

Br J Nutr. 2014 Nov 14;112(9):1510-20. doi: 10.1017/S0007114514002384. Epub 2014 Sep 18.

Calcium supplementation and bone mineral accretion in Chinese adolescents aged 12-14 years: a 12-month, dose-response, randomised intervention trial.

Ma XM[1], Huang ZW[2], Yang XG[2], Su YX[1].

Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Department of Nutrition, School of Public Health, Sun Yat-sen University,Guangzhou510080,People's Republic of China; Key Lab of Trace Element Nutrition of Ministry of Health, National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention,Beijing100021,People's Republic of China.

Abstract

A 12-month, dose-response, randomised, intervention trial was conducted to determine adequate Ca intake levels for Chinese adolescents by investigating the effect of Ca supplementation on bone mineral accretion. A total of 220 Han adolescents (111 girls and 109 boys) aged 12-14 years were recruited. All subjects were randomly divided into three groups. The bone mineral content (BMC) and bone mineral density (BMD) of the whole body, lumbar spine (L1-L4), left hip and femoral neck were measured by dual-energy X-ray absorptiometry. Girls in the high-Ca group (actual Ca intake: 1243 (sd 193) mg/d) exhibited greater increases in the femoral neck BMC compared with those in the low-Ca group (9·7 v. 6·4 %, P =0·04) over the 1-year intervention period. The increases in femoral neck BMC were greater in boys in the high-Ca and medium-Ca groups (actual Ca intake: 985 (sd 168) mg/d) than in those in the low-Ca group (15·7 v. 11·7 %, P =0·03; 15·8 v. 11·7 %, P =0·03). Ca supplementation had significant effects on the whole-body BMC and BMD in subjects with physical activity levels>34·86 metabolic equivalents and on the spine BMD and BMC and BMD of most sites in subjects with Tanner stage < 3. Increasing Ca intake levels with Ca supplementation enhanced femoral neck mineral acquisition in Chinese adolescents. Furthermore, high physical activity levels and low Tanner stage appeared to significantly contribute to the effect of Ca supplementation on bone mass. Whether this is a lasting beneficial effect leading to the optimisation of peak bone mass needs to be determined in other long-term prospective studies.

Homeopathy. 2014 Oct;103(4):224-31. doi: 10.1016/j.homp.2014.08.004. Epub 2014 Sep 27.

Efficacy of homeopathic intervention in subclinical hypothyroidism with or without autoimmune thyroiditis in children: an exploratory randomized control study.

Chauhan VK[1], Manchanda RK[2], Narang A[3], Marwaha RK[4], Arora S[5], Nagpal L[6], Verma SK[7], Sreenivas V[8].

Dr. B. R. Sur Homoeopathic Medical College, Hospital & Research Centre, New Delhi, India. Electronic address; Central Council for Research in Homoeopathy, Department of AYUSH, Ministry of Health & Family Welfare, Government of India, India; Institute of Nuclear Medicine and Allied Sciences, New Delhi, India; Directorate of Indian System of Medicine & Homeopathy, Government of NCT of Delhi, New Delhi, India; All India Institute of Medical Sciences, New Delhi, India.

INTRODUCTION:

The decision to treat subclinical hypothyroidism (SCH) with or without autoimmune thyroiditis (AIT) in children, presents a clinical dilemma. This study was undertaken to evaluate the efficacy of individualized homeopathy in these cases.

METHODS:

The study is an exploratory, randomized, placebo controlled, single blind trial. Out of 5059 school children (06-18 years) screened for thyroid disorders, 537 children had SCH/AIT and 194 consented to participate. Based on primary outcome measures (TSH and/or antiTPOab) three major groups were formed: Group A - SCH + AIT (n = 38; high TSH with antiTPOab+), Group B - AIT (n = 47; normal TSH with antiTPOab+) and Group C - SCH (n = 109; only high TSH) and were further randomized to two subgroups-verum and control. Individualized homeopathy or identical placebo was given to respective subgroup. 162 patients completed 18 months of study.

RESULTS:

Baseline characteristics were similar in all the subgroups. The post treatment serum TSH (Group A and C) returned to normal limits in 85.94% of verum and 64.29% of controls ($p < 0.006$), while serum AntiTPOab titers (Group A and B) returned within normal limits in 70.27%of verum and 27.02%controls ($p < 0.05$). Eight children (10.5%) progressed to overt hypothyroidism (OH) from control group.

CONCLUSION:

A statistically significant decline in serum TSH values and antiTPOab titers indicates that the homeopathic intervention has not only the potential to treat SCH with or without antiTPOab but may also prevent progression to OH.

Enterovirus infections

Emerg Infect Dis. 2015 Jan;21(1). doi: 10.3201/eid2101.140992.

Workshop on use of intravenous immunoglobulin in hand, foot and mouth disease in Southeast Asia.

Chea S, Cheng YB, Chokephaibulkit K, Chotpitayasunondh T, Rogier van Doorn H, Hafy Z, Kawichai S, Liu CC, Nam NT, Ooi MH, Wolbers M, Zeng M.

Abstract

The South East Asia Infectious Disease Clinical Research Network convened subject matter experts at a workshop to make consensus recommendations for study design of a clinical trial for use of intravenous immunoglobulin (IVIg) in severe hand, foot and mouth disease (HFMD). HFMD is a highly contagious emerging infection among children in the region, a small proportion of whom develop neurologic and cardiopulmonary complications with high case-fatality rates. The use of IVIg for treatment of severe disease is widespread and a part of local, national, and international guidelines, but no clinical evidence warrants the use of this drug, which is expensive and has potentially serious side effects. During a 2-day workshop in March 2014, a group of HFMD experts reviewed the current evidence related to use of IVIg in HFMD and discussed potential study design, feasibility, inclusion and exclusion criteria, sample size, primary and secondary endpoints, and subsidiary studies for a randomized, placebo-controlled trial.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4285270/

Epilepsy and acute seizures

J Child Neurol. 2014 Jul;29(7):895-902. doi: 10.1177/0883073813493501. Epub 2013 Jul 31.

Efficacy of sublingual lorazepam versus intrarectal diazepam for prolonged convulsions in Sub-Saharan Africa.

Malu CK[1], Kahamba DM[2], Walker TD[3], Mukampunga C[4], Musalu EM[5], Kokolomani J[5], Mayamba RM[6], Wilmshurst JM[7], Dubru JM[8], Misson JP[8].

Service of Child Neurology, Kinshasa University Teaching Hospital, Democratic Republic of Congo; Service of Internal Medicine, Butare University Teaching Hospital, Rwanda; Service of Pediatrics, Butare University Teaching Hospital, Rwanda; School of Public health, Kinshasa University Teaching Hospital, Democratic Republic of Congo; Service of Neurology, St Joseph Hospital, Mons, Belgium; Department of Pediatric Neurology, Red Cross Children's Hospital, School of Child and Adolescent Health, University of Cape Town, South Africa; Service of Paediatrics and Child Neurology, CHR Citadelle Hospital and CHU University Hospital, University of Liège, Belgium.

Abstract

In Sub-Saharan Africa, intrarectal diazepam is the first-line anticonvulsant mostly used in children. We aimed to assess this standard care against sublingual lorazepam, a medication potentially as effective and safe, but easier to administer. A randomized controlled trial was conducted in the pediatric emergency departments of 9 hospitals. A total of 436 children aged 5 months to 10 years with convulsions persisting for more than 5 minutes were assigned to receive intrarectal diazepam (0.5 mg/kg, n = 202) or sublingual lorazepam (0.1 mg/kg, n = 234). Sublingual lorazepam stopped seizures within 10 minutes of administration in 56% of children compared with intrarectal diazepam in 79% (P < .001). The probability of treatment failure is higher in case of sublingual lorazepam use (OR = 2.95, 95% CI = 1.91-4.55). Sublingual lorazepam is less efficacious in stopping pediatric seizures than intrarectal diazepam, and intrarectal diazepam should thus be preferred as a first-line medication in this setting.

Epilepsy Res. 2014 Oct;108(8):1444-50. doi: 10.1016/j.eplepsyres.2014.06.014. Epub 2014 Jul 6.

Growth parameters and childhood epilepsy in Hai District, Tanzania: a community-based study.

Rogathe JJ[1], Todd J[2], Hunter E[3], Walker R[4], Ngugi A[5], Newton C[6], Burton K[7].

Kilimanjaro Christian Medical University College, Moshi, Tanzania; National Institute for Medical Research, Mwanza, Tanzania; Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Tropical Medicine, London, UK; Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital, North Shields, UK; Centre for Geographical Medice (Coast), Kenya Medical Research Institute, Kilifi, Kenya; Department of Paediatrics, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania; Department of Psychiatry, University of Oxford, Oxford, UK; Neurosciences Unit, Institute of Child Health, University College London, London, UK. Electronic address: kjburton@doctors.org.uk.

AIM:

This cross-sectional study examined whether growth parameters were associated with epilepsy in children living in a rural community in sub-Saharan Africa (SSA).

MATERIALS AND METHODS:

A cross-sectional study was performed in the Hai District Demographic Surveillance Site (HDSS), Tanzania in which 6-14 year old children with epilepsy (CWE) were identified. Age matched controls were randomly selected from the Hai census database for comparison. Anthropometric measurements were used to assess the nutritional status of the children and body mass index (BMI) calculated. Associations between social, demographic and nutritional factors and epilepsy were assessed using multivariable logistic regression.

RESULTS:

112 CWE were identified and were compared with 113 controls. There was no significant difference in the BMI between cases and controls (T-test, p-value of 0.117). Amongst cases, there were no significant associations between BMI and motor difficulties, antiepileptic drug use, cognitive or behavioural problems, early-onset epilepsy or seizure frequency. In the whole group, BMI was significantly associated with socio-economic status (p=0.037) and age.

DISCUSSION:

There was no significant difference found between CWE and matched controls with respect to nutritional status. This suggests that there is no causal association between under nutrition and epilepsy in this community. Nutritional assessment is still important as part of the comprehensive care of CWE.

Epilepsy Res. 2014 Oct;108(8):1451-60. doi: 10.1016/j.eplepsyres.2014.07.004. Epub 2014 Jul 23.

Prevalence and neuro-psychiatric comorbidities of pediatric epilepsy in Taiwan: a national population-based study.

Chiang KL[1], Cheng CY[2].

Department of Pediatric Neurology, Kuang-Tien General Hospital; Program of Health Administration, Tunghai University, No. 181, Section 3, Taichung Harbor Road, Taichung, 407-04, Taiwan ROC

OBJECTIVE:

Children with epilepsy may have comorbidities that result in significant disability. Epidemiological information for pediatric patients with epilepsy in Taiwan is scant. This research estimates the prevalence and common neuro-psychiatric comorbidities of children with epilepsy in Taiwan.

METHODS:

Patients aged less than 20 years old who had received a diagnosis of epilepsy and suffered from epileptic seizures in 2005 were identified in the NHIRD based on ICD-9-CM and prescription records for the use of at least one AED. We used cases of epileptic seizure to survey outpatient service data, and identify common neuro-psychiatric comorbidities. The crude prevalence rate and the age- and sex-specific prevalence were estimated. We also examined the effects of urbanization.

RESULTS:

The estimated prevalence of epilepsy was 0.33% in the pediatric population, with 0.29% for girls and 0.36% for boys. The most common neuropsychiatric comorbidities were learning disability and developmental delay, cerebral palsy, and mental retardation. Epilepsy was more prevalent in boys than in girls, especially among infants, preschool children, and those living in rural areas. In addition, boys with epilepsy had a higher rate of neurological comorbidities. The prevalence of psychiatric comorbidities was lower than that reported in previous studies performed in other countries, especially among children with epilepsy living in rural areas.

CONCLUSION:

This research provides the largest nationwide, population-based study of childhood epilepsy to estimate the prevalence and the associated neuropsychiatric comorbidities of pediatric epilepsy in Taiwan. Potential rural-urban disparity basing on prevalence and associated neuropsychiatric comorbidities cannot be ignored in Taiwan.

Epilepsy Res. 2014 Oct;108(8):1378-84. doi: 10.1016/j.eplepsyres.2014.06.019. Epub 2014 Jul 5.

High dose (4 mg/kg/day) versus usual dose (2 mg/kg/day) oral prednisolone for treatment of infantile spasms: an open-label, randomized controlled trial.

Chellamuthu P[1], Sharma S[2], Jain P[3], Kaushik JS[4], Seth A[5], Aneja S[2].

Department of Pediatrics and Neurology, Lady Hardinge Medical College and Associated Kalawati Saran Children's Hospital, New Delhi 110001, India; Division of Pediatric Neurology, Department of Pediatrics, BLK Super Speciality Hospital, Pusa Road, New Delhi, India.

OBJECTIVES:

This study aimed to test the hypothesis that high-dose prednisolone (4 mg/kg/day) may be more efficacious than usual-dose (2 mg/kg/day) prednisolone for spasm resolution at 14-days in children with infantile spasms.

METHODS:

This was a randomized, open-label-trial conducted at a tertiary-level-hospital from February-2012 to March-2013. Children aged 3-months to 2-years presenting with infantile spasms in clusters (at least 1 cluster/day) with hypsarrhythmia or its variants on EEG were enrolled. The study participants were randomized to receive either high-dose prednisolone (4 mg/kg/day) or the usual-dose (2 mg/kg/day) prednisolone. The primary outcome measure was the proportion of children who achieved spasm freedom for 48-h at day-14 after treatment initiation as per parental reports in both the groups. The adverse effects were also monitored. The study was registered with the clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01575639).

RESULTS:

Sixty-three children were randomized into the two groups with comparable baseline characteristics. The proportion of children with spasm cessation on day-14 was significantly higher in the high-dose group as compared to the usual-dose group (51.6% vs. 25%, p=0.03). The absolute risk reduction was 26.6% (95% confidence interval 11.5-41.7%) with number needed to treat being 4. The adverse effects were comparable in both the groups.

CONCLUSIONS:

High-dose prednisolone (4 mg/kg/d) was more effective than low-dose prednisolone (2mg/kg/d) in achieving spasm cessation at 14-days (as per parental reports) in children with infantile spasms.

Hygiene and environmental health

Am J Trop Med Hyg. 2015 Feb;92(2):437-47. doi: 10.4269/ajtmh.14-0138. Epub 2014 Nov 24.

Pilot cluster randomized controlled trials to evaluate adoption of water, sanitation, and hygiene interventions and their combination in rural western Kenya.

Christensen G[1], Dentz HN[2], Pickering AJ[2], Bourdier T[2], Arnold BF[2], Colford JM Jr[2], Null C[2].

Rollins School of Public Health, Emory University, Atlanta, Georgia; Innovations for Poverty Action, Busia, Kenya; Department of Civil and Environmental Engineering, Stanford University, Stanford, California; Division of Epidemiology, University of California, Berkeley, California

In preparation for a larger trial, the Water, Sanitation, and Hygiene (WASH) Benefits pilot study enrolled 72 villages and 499 subjects in two closely related randomized trials of WASH interventions in rural western Kenya. Intervention households received hardware and promotion for one of the following: water treatment, sanitation and latrine improvements, handwashing with soap, or the combination of all three. Interventions were clustered by village. A follow-up survey was conducted 4 months after intervention delivery to assess uptake. Intervention

households were significantly more likely than controls to have chlorinated stored water (36-60 percentage point increases), covers over latrine drop holes (55-75 percentage point increases), less stool visible on latrine floors (16-47 percentage point reductions), and a place for handwashing (71-85 percentage point increases) with soap available (49-66 percentage point increases). The high uptake in all arms shows that combined interventions can achieve high short-term adoption rates if well-designed.

PLoS Med. 2014 Aug 26;11(8):e1001709. doi: 10.1371/journal.pmed.1001709. eCollection 2014.

The effect of India's total sanitation campaign on defecation behaviors and child health in rural Madhya Pradesh: a cluster randomized controlled trial.

Patil SR[1], Arnold BF[2], Salvatore AL[3], Briceno B[4], Ganguly S[5], Colford JM Jr[2], Gertler PJ[6].

Network for Engineering and Economics Research and Management (NEERMAN), Mumbai, Maharashtra, India; School of Public Health, University of California, Berkeley, California, USA; Stanford School of Medicine, Stanford University, Stanford, California, USA; Water and Sanitation Program, the World Bank, Washington (D.C.); National Institute for Cholera and Enteric Diseases, Kolkata, West Bengal, India.

BACKGROUND:

Poor sanitation is thought to be a major cause of enteric infections among young children. However, there are no previously published randomized trials to measure the health impacts of large-scale sanitation programs. India's Total Sanitation Campaign (TSC) is one such program that seeks to end the practice of open defecation by changing social norms and behaviors, and providing technical support and financial subsidies. The objective of this study was to measure the effect of the TSC implemented with capacity building support from the World Bank's Water and Sanitation Program in Madhya Pradesh on availability of individual household latrines (IHLs), defecation behaviors, and child health (diarrhea, highly credible gastrointestinal illness [HCGI], parasitic infections, anemia, growth).

METHODS AND FINDINGS:

We conducted a cluster-randomized, controlled trial in 80 rural villages. Field staff collected baseline measures of sanitation conditions, behaviors, and child health (May-July 2009), and revisited households 21 months later (February-April 2011) after the program was delivered. The study enrolled a random sample of 5,209 children <5 years old from 3,039 households that had at least one child <24 months at the beginning of the study. A random subsample of 1,150 children <24 months at enrollment were tested for soil transmitted helminth and protozoan infections in stool. The randomization successfully balanced intervention and control groups, and we estimated differences between groups in an intention to treat analysis. The intervention increased percentage of households in a village with improved sanitation facilities as defined by the WHO/UNICEF Joint Monitoring Programme by an average of 19% (95% CI for difference: 12%-26%; group means: 22% control versus 41% intervention), decreased open defecation among adults by an average of 10% (95% CI for difference: 4%-15%; group means: 73% intervention versus 84% control). However, the intervention did not improve child health measured in terms of multiple health outcomes (diarrhea, HCGI, helminth infections, anemia, growth). Limitations of the study included a relatively short follow-up period following

implementation, evidence for contamination in ten of the 40 control villages, and bias possible in self-reported outcomes for diarrhea, HCGI, and open defecation behaviors.

CONCLUSIONS:

The intervention led to modest increases in availability of IHLs and even more modest reductions in open defecation. These improvements were insufficient to improve child health outcomes (diarrhea, HCGI, parasite infection, anemia, growth). The results underscore the difficulty of achieving adequately large improvements in sanitation levels to deliver expected health benefits within large-scale rural sanitation programs.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4144850/pdf/pmed.1001709.pdf

Trop Med Int Health. 2014 Oct;19(10):1185-97. doi: 10.1111/tmi.12360. Epub 2014 Jul 24.

Assessing the impact of a school-based latrine cleaning and handwashing program on pupil absence in Nyanza Province, Kenya: a cluster-randomized trial.

Caruso BA[1], Freeman MC, Garn JV, Dreibelbis R, Saboori S, Muga R, Rheingans R.

Department of Behavioral Sciences and Health Education, Emory University, Atlanta, GA, USA; Center for Global Safe Water at Emory University, Atlanta, GA, USA.

OBJECTIVES:

Improving school water, sanitation and hygiene (WASH) conditions reduces pupil absence and illness. However, these benefits may depend on the conditions of the latrines and availability of consumables. We sought to determine whether a low-cost, policy-relevant, environmental-level latrine cleaning intervention could improve latrine cleanliness, increase its use and reduce absenteeism.

METHODS:

In a three-arm, cluster-randomized trial we assessed absence via periodical roll-call among 17 564 pupils in 60 schools that had previously received WASH improvements as part of the SWASH+ project. Latrine conditions and use were also assessed using structured observation. Latrine cleanliness increased significantly during the post-intervention period among schools receiving the latrine cleaning package compared to controls, as did handwashing with soap. We found no difference in latrine use and absence across arms.

CONCLUSIONS:

The additive impact of cleaning may not have been strong enough to impact absence above and beyond reductions attributable to the original WASH infrastructure improvements and basic hygiene education the schools previously received. Improving latrine conditions is important for the dignity and well-being of pupils, and investments and strategies are necessary to ensure that school toilets are clean and pupil-friendly.

Am J Trop Med Hyg. 2014 Aug;91(2):415-23. doi: 10.4269/ajtmh.13-0475. Epub 2014 Jun 9.

Microbiological evaluation of the efficacy of soapy water to clean hands: a randomized, non-inferiority field trial.

Amin N[1], Pickering AJ[2], Ram PK[2], Unicomb L[2], Najnin N[2], Homaira N[2], Ashraf S[2], Abedin J[2], Islam MS[2], Luby SP[2].

International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh; Stanford University, Stanford, California; University at Buffalo, Buffalo, New York; Centers for Disease Control and Prevention, Atlanta

Abstract

We conducted a randomized, non-inferiority field trial in urban Dhaka, Bangladesh among mothers to compare microbial efficacy of soapy water (30 g powdered detergent in 1.5 L water) with bar soap and water alone. Fieldworkers collected hand rinse samples before and after the following washing regimens: scrubbing with soapy water for 15 and 30 seconds; scrubbing with bar soap for 15 and 30 seconds; and scrubbing with water alone for 15 seconds. Soapy water and bar soap removed thermotolerant coliforms similarly after washing for 15 seconds (mean log10 reduction = 0.7 colony-forming units [CFU], $P < 0.001$ for soapy water; mean log10 reduction = 0.6 CFU, $P = 0.001$ for bar soap). Increasing scrubbing time to 30 seconds did not improve removal ($P > 0.05$). Scrubbing hands with water alone also reduced thermotolerant coliforms (mean log10 reduction = 0.3 CFU, $P = 0.046$) but was less efficacious than scrubbing hands with soapy water. Soapy water is an inexpensive and microbiologically effective cleansing agent to improve handwashing among households with vulnerable children.

Haematological disorders

(See also Malaria: treatment of uncomplicated malaria for study in sickle-cell disease patients)

Hemoglobin. 2014;38(5):359-64. doi: 10.3109/03630269.2014.951890. Epub 2014 Sep 15.

N-Acetylcysteine supplementation reduces oxidative stress and DNA damage in children with β-thalassemia.

Ozdemir ZC[1], Koc A, Aycicek A, Kocyigit A.

Pediatric Hematology Department, Harran University, Medical Faculty, Sanlıurfa, Turkey

Abstract

There are several reports that increased oxidative stress and DNA damage were found in β-thalassemia major (β-TM) patients. In this study, we aimed to evaluate the effects of N-acetylcysteine (NAC) and vitamin E on total oxidative stress and DNA damage in children with β-TM. Seventy-five children with transfusion-dependent β-thalassemia (β-thal) were randomly chosen to receive 10 mg/kg/day of NAC or 10 IU/kg/day of vitamin E or no supplementation; 28 healthy controls were also included in the study. Serum total oxidant status (TOS) and total antioxidant capacity (TAC) were measured, oxidative stress index (OSI) was calculated, and mononuclear DNA damage was assessed by alkaline comet assay; they were determined before treatment and after 3 months of treatment. Total oxydent status, OSI, and DNA damage levels were significantly higher and TAC levels were significantly lower in the thalassemic children than in the healthy controls ($p < 0.001$). In both supplemented groups, mean TOS and OSI levels

were decreased; TAC and pre transfusion hemoglobin (Hb) levels were significantly increased after 3 months ($p \leq 0.002$). In the NAC group, DNA damage score decreased ($p = 0.001$). N-Acetylcysteine and vitamin E may be effective in reducing serum oxidative stress and increase pre transfusion Hb levels in children with β-thal. N-Acetylcysteine also can reduce DNA damage.

In Vivo. 2014 Jul-Aug;28(4):645-9.

Combined versus monotherapy or concurrent therapy for treatment of thalassaemia.

Song TS[1], Hsieh YW[2], Peng CT[3], Chen TL[4], Lee HZ[5], Chung JG[6], Hour MJ[7].

School of Pharmacy, China Medical University, Taichung, Department of Pediatrics, Children's Hospital, China Medical University; Department of Biotechnology, Asia University, Taichung; Institute of Biochemistry and Molecular Biology, National Yang-Ming University, Taipei, Taiwan, R.O.C.

Abstract

A combined deferasirox (DFX) and deferiprone (DFP) treatment protocol for relieving thalassemia patients' iron-overload was designed and the pharmacokinetic study was performed by LC-MS/MS. For this open-label, randomized trial, eight patients were recruited and randomly allocated to different treatment regimens: (A) monotherapy with single oral dose of DFX 30 mg/kg, (B) monotherapy with DFP 80 mg/kg/day, twice daily, (C) combined therapy with DFX and DFP (DFX 30 mg/kg for first dose, DFP 40 mg/kg 7 hours later, and DFP 40 mg/kg after another 7 h) and (D) concurrent therapy with DFX 30 mg/kg and DFP 80 mg/kg. Descriptive statistics evaluated pharmacokinetic parameters, AUC0-t, AUC0-inf, Cmax, Tmax, T1/2 and MRT. A positive pharmacokinetic drug interaction was observed in combined therapy. In case of DFX, combined therapy tallied about 2-fold larger than monotherapy in AUC, 1.5-fold larger in Cmax, 1 h longer in Tmax, but 1 h shorter in T1/2. Regarding DFP, most such parameters of combined therapy concurred with monotherapy. Conversely, negative drug interaction was observed in concurrent therapy. With DFX, concurrent therapy attained 1.2- to 2.2-fold lower than monotherapy in AUC0-t and Cmax, 0.6-h shorter in Tmax, and 3-fold longer in T1/2. With DFP, concurrent therapy proved approximately 2-fold larger than monotherapy in AUC and Cmax, 2.5-fold longer in T1/2, and 1.4-fold longer in MRT. Follow-up of subjects' clinical examinations and subjective symptoms showed no adverse events. Our findings showed the combined therapy had advantages, safe, convenient and painless for patients, over the existing concurrent therapy with deferoxamine (DFO) and DFX.

KEYWORDS:

Combined therapy; LC-MS/MS; deferasirox (DFX); deferiprone (DFP); pharmacokinetics; thalassaemia patients

Blood. 2014 Dec 18;124(26):3880-6. doi: 10.1182/blood-2014-05-573055. Epub 2014 Sep 26.

Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial.

Collins PW[1], Young G[2], Knobe K[3], Karim FA[4], Angchaisuksiri P[5], Banner C[6], Gürsel T[7], Mahlangu J[8], Matsushita T[9], Mauser-Bunschoten EP[10], Oldenburg J[11], Walsh CE[12], Negrier C[13]; paradigm 2 Investigators.

Arthur Bloom Haemophilia Centre, Institute of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, United Kingdom; Hemostasis and Thrombosis Center, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA; Haemophilia R&D Portfolio, Novo Nordisk A/S, Soeborg, Denmark; Haemophilia Centre, National Blood Centre, Kuala Lumpur, Malaysia; Division of Hematology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; Gazi University Medical School, Ankara, Turkey; Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, National Health Laboratory Services and University of the Witwatersrand, Johannesburg, South Africa; Department of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan; Van Creveldkliniek, University Medical Centre, Utrecht, The Netherlands; Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany; Division of Hematology and Medical Oncology, Mount Sinai Medical Center, New York, NY; and Hôpital Edouard Herriot, University Claude Bernard Lyon 1, Lyon, France.

Abstract

This multinational, randomized, single-blind trial investigated the safety and efficacy of nonacog beta pegol, a recombinant glycoPEGylated factor IX (FIX) with extended half-life, in 74 previously treated patients with hemophilia B (FIX activity ≤2 IU/dL). Patients received prophylaxis for 52 weeks, randomized to either 10 IU/kg or 40 IU/kg once weekly or to on-demand treatment of 28 weeks. No patients developed inhibitors, and no safety concerns were identified. Three hundred forty-five bleeding episodes were treated, with an estimated success rate of 92.2%. The median annualized bleeding rates (ABRs) were 1.04 in the 40 IU/kg prophylaxis group, 2.93 in the 10 IU/kg prophylaxis group, and 15.58 in the on-demand treatment group. In the 40 IU/kg group, 10 (66.7%) of 15 patients experienced no bleeding episodes into target joints compared with 1 (7.7%) of 13 patients in the 10 IU/kg group. Health-related quality of life (HR-QoL) assessed with the EuroQoL-5 Dimensions visual analog scale score improved from a median of 75 to 90 in the 40 IU/kg prophylaxis group. Nonacog beta pegol was well tolerated and efficacious for the treatment of bleeding episodes and was associated with low ABRs in patients receiving prophylaxis. Once-weekly prophylaxis with 40 IU/kg resolved target joint bleeds in 66.7% of the affected patients and improved HR-QoL

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4271178/

HIV / AIDS

Ante-retroviral therapy (ART)

N Engl J Med. 2014 Jul 17;371(3):234-47. doi: 10.1056/NEJMoa1311274.

Assessment of second-line antiretroviral regimens for HIV therapy in Africa.

Paton NI, Kityo C, Hoppe A, Reid A, Kambugu A, Lugemwa A, van Oosterhout JJ, Kiconco M, Siika A, Mwebaze R, Abwola M, Abongomera G, Mweemba A, Alima H, Atwongyeire D, Nyirenda R, Boles J, Thompson J, Tumukunde D, Chidziva E, Mambule I, Arribas JR, Easterbrook PJ, Hakim J, Walker AS, Mugyenyi P; EARNEST Trial Team.

BACKGROUND:

The efficacy and toxic effects of nucleoside reverse-transcriptase inhibitors (NRTIs) are uncertain when these agents are used with a protease inhibitor in second-line therapy for human immunodeficiency virus (HIV) infection in resource-limited settings. Removing the NRTIs or replacing them with raltegravir may provide a benefit.

METHODS:

In this open-label trial in sub-Saharan Africa, we randomly assigned 1277 adults and adolescents with HIV infection and first-line treatment failure to receive a ritonavir-boosted protease inhibitor (lopinavir-ritonavir) plus clinician-selected NRTIs (NRTI group, 426 patients), a protease inhibitor plus raltegravir in a superiority comparison (raltegravir group, 433 patients), or protease-inhibitor monotherapy after 12 weeks of induction therapy with raltegravir in a noninferiority comparison (monotherapy group, 418 patients). The primary composite end point, good HIV disease control, was defined as survival with no new World Health Organization stage 4 events, a CD4+ count of more than 250 cells per cubic millimeter, and a viral load of less than 10,000 copies per milliliter or 10,000 copies or more with no protease resistance mutations at week 96 and was analyzed with the use of imputation of data (≤4%).

RESULTS:

Good HIV disease control was achieved in 60% of the patients (mean, 255 patients) in the NRTI group, 64% of the patients (mean, 277) in the raltegravir group (P=0.21 for the comparison with the NRTI group; superiority of raltegravir not shown), and 55% of the patients (mean, 232) in the monotherapy group (noninferiority of monotherapy not shown, based on a 10-percentage-point margin). There was no significant difference in rates of grade 3 or 4 adverse events among the three groups (P=0.82). The viral load was less than 400 copies per milliliter in 86% of patients in the NRTI group, 86% in the raltegravir group (P=0.97), and 61% in the monotherapy group (P<0.001).

CONCLUSIONS:

When given with a protease inhibitor in second-line therapy, NRTIs retained substantial virologic activity without evidence of increased toxicity, and there was no advantage to replacing them with raltegravir. Virologic control was inferior with protease-inhibitor monotherapy.

http://www.nejm.org/doi/pdf/10.1056/NEJMoa1311274

Early infant diagnosis

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

Management of HIV-related conditions

AIDS. 2014 Jul;28 Suppl 3:S347-57. doi: 10.1097/QAD.0000000000000335.

A randomized clinical trial of an intervention to promote resilience in young children of HIV-positive mothers in South Africa.

Eloff I[1], Finestone M, Makin JD, Boeving-Allen A, Visser M, Ebersöhn L, Ferreira R, Sikkema KJ, Briggs-Gowan MJ, Forsyth BW.

Faculty of Education, Department of Obstetrics and Gynaecology, University of Pretoria, Pretoria, South Africa; Department of Pediatrics, Wake Forest University, Winston-Salem, North Carolina, USA; Department of Psychology, University of Pretoria, Pretoria, South Africa; Department of Psychology and Neuroscience, and Global Health, Duke University, Durham, North Carolina; Department of Psychiatry, University of Connecticut Health Center, Farmington; Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA.

OBJECTIVE:

The objective of this study is to assess the efficacy of an intervention designed to promote resilience in young children living with their HIV-positive mothers.

DESIGN/METHODS:

HIV-positive women attending clinics in Tshwane, South Africa, and their children, aged 6-10 years, were randomized to the intervention (I) or standard care (S). The intervention consisted of 24 weekly group sessions led by community care workers. Mothers and children were in separate groups for 14 sessions, followed by 10 interactive sessions. The primary focus was on parent-child communication and parenting. Assessments were completed by mothers and children at baseline and 6, 12 and 18 months. Repeated mixed linear analyses were used to assess change over time.

RESULTS:

Of 390 mother-child pairs, 84.6% (I: 161 and S: 169) completed at least two interviews and were included in the analyses. Children's mean age was 8.4 years and 42% of mothers had been ill in the prior 3 months. Attendance in groups was variable: only 45.7% attended more than 16 sessions. Intervention mothers reported significant improvements in children's externalizing behaviours (ß = -2.8, P = 0.002), communication (ß = 4.3, P = 0.025) and daily living skills (ß = 5.9, P = 0.024), although improvement in internalizing behaviours and socialization was not significant (P = 0.061 and 0.052, respectively). Intervention children reported a temporary increase in anxiety but did not report differences in depression or emotional intelligence.

CONCLUSION:

This is the first study demonstrating benefits of an intervention designed to promote resilience among young children of HIV-positive mothers. The intervention was specifically designed for an African context and has the potential to benefit large numbers of children, if it can be widely implemented.

Nutrition, growth and development of children with HIV

Am J Clin Nutr. 2014 Dec;100(6):1559-68. doi: 10.3945/ajcn.113.082149. Epub 2014 Oct 22.

Morbidity in relation to feeding mode in African HIV-exposed, uninfected infants during the first 6 mo of life: the Kesho Bora study.

Bork KA[1], Cournil A[1], Read JS[1], Newell ML[1], Cames C[1], Meda N[1], Luchters S[1], Mbatia G[1], Naidu K[1], Gaillard P[1], de Vincenzi I[1].

Institut de Recherche pour le Développement (IRD), UMI233 IRD/Université de Montpellier 1, Montpellier, France (KAB, AC, and CC); the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD (JSR); the Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa (M-LN); the Centre Muraz, Bobo-Dioulasso, Burkina Faso (NM); the International Centre for Reproductive Health, Mombasa, Kenya (SL); the Kenyatta National Hospital and University of Nairobi, Nairobi, Kenya (GM); the University of KwaZulu-Natal, Durban, South African Republic (KN); and the WHO, Reproductive Health and Research, Geneva, Switzerland (PG and IdV).

BACKGROUND:

Refraining from breastfeeding to prevent HIV transmission has been associated with increased morbidity and mortality in HIV-exposed African infants.

OBJECTIVE:

The objective was to assess risks of common and serious infectious morbidity by feeding mode in HIV-exposed, uninfected infants ≤6 mo of age with special attention to the issue of reverse causality.

DESIGN:

HIV-infected pregnant women from 5 sites in Burkina Faso, Kenya, and South Africa were enrolled in the prevention of mother-to-child transmission Kesho Bora trial and counseled to either breastfeed exclusively and cease by 6 mo postpartum or formula feed exclusively. Maternal-reported morbidity (fever, diarrhea, and vomiting) and serious infectious events (SIEs) (gastroenteritis and lower respiratory tract infections) were investigated for 751 infants for 2 age periods (0-2.9 and 3-6 mo) by using generalized linear mixed models with breastfeeding as a time-dependent variable and adjustment for study site, maternal education, economic level, and cotrimoxazole prophylaxis.

RESULTS:

Reported morbidity was not significantly higher in nonbreastfed compared with breastfed infants [OR: 1.31 (95% CI: 0.97, 1.75) and 1.21 (0.90, 1.62) at 0-2.9 and 3-6 mo of age, respectively]. Between 0 and 2.9 mo of age, never-breastfed infants had increased risks of morbidity compared with those of infants who were exclusively breastfed (OR: 1.49; 95% CI: 1.01, 2.2; P = 0.042). The adjusted excess risk of SIEs in nonbreastfed infants was large between 0 and 2.9 mo (OR: 6.0; 95% CI: 2.2, 16.4; P = 0.001). Between 3 and 6 mo, the OR for SIEs was sensitive to the timing of breastfeeding status, i.e., 4.3 (95% CI: 1.2, 15.3; P = 0.02) when defined at end of monthly intervals and 2.0 (95% CI: 0.8, 5.0; P = 0.13) when defined at the beginning of intervals. Of 52 SIEs, 3 mothers reported changes in feeding mode during the SIE although none of the mothers ceased breastfeeding completely.

CONCLUSIONS:

Not breastfeeding was associated with increased risk of serious infections especially between 0 and 2.9 mo of age. The randomized controlled trial component of the Kesho Bora study was registered at Current Controlled Trials (www.controlled-trials.com) as ISRCTN71468401.

Prevention of parent to child transmission of HIV

Implement Sci. 2015 Apr 30;10(1):61. doi: 10.1186/s13012-015-0249-6.

Early ART initiation among HIV-positive pregnant women in central Mozambique: a stepped wedge randomized controlled trial of an optimized Option B+ approach.

Cowan JF[1,2], Micek M[3], Cowan JF[4,5], Napúa M[6], Hoek R[7], Gimbel S[8,9,10], Gloyd S[11,12], Sherr K[13,14], Pfeiffer JT[15,16,17], Chapman RR[18,19,20].

Department of Global Health, University of Washington Schools of Medicine and Public Health, Health Alliance International (HAI); Department of Family Medicine, University of Washington; Beira Operations Research Center, Ministry of Health, Ponta Gea, Beira, Mozambique; Department of Family and Child Nursing, University of Washington; Department of Anthropology, University of Washington.

BACKGROUND:

Despite effective prevention strategies and increasing investments in global health, maternal to child transmission (MTCT) of HIV remains a significant problem globally, especially in sub-Saharan Africa. In 2012, there were 94,000 HIV-positive pregnant women in Mozambique. Approximately 15% of these women transmitted HIV to their newborn infants, resulting in nearly 14,000 new pediatric HIV infections that year. To address this issue, in 2013, the Mozambican Ministry of Health implemented the World Health Organization-recommended "Option B+" strategy in which all newly diagnosed HIV-positive pregnant women are counseled to initiate combination anti-retroviral therapy (ART) immediately upon diagnosis regardless of CD4 count and to continue treatment for life. Given the limited experience with Option B+ in sub-Saharan Africa, few rigorous pragmatic trials have studied this new treatment strategy.

METHODS:

This study utilizes an initial formative research process involving patient and health care provider interviews and focus groups, workforce assessments, value stream mapping, and commodity utilization assessments to understand the strengths and weaknesses in the current Option B+ care cascade. The formative research is intended to guide identification and prioritization of key workflow modifications and the development of an enhanced adherence and retention package. These two components are bundled into a defined intervention implemented and evaluated across six health facilities utilizing a stepped wedge randomized controlled trial study design. The overall objective of this trial is to develop and test a pilot intervention in central Mozambique to implement the new Option B+ guidelines with high fidelity and increase the proportion of HIV-positive pregnant women in target antenatal clinics (ANC) who start ART prior to delivery and are retained in care.

DISCUSSION:

This pragmatic study utilizes research strategies that have the potential to meaningfully improve the Option B+ care cascade in central Mozambique and to decrease the MTCT of HIV. This trial is designed to identify critical low-cost improvement strategies that can be bundled into a defined intervention. If this intervention has a measurable impact, it can be rapidly scaled up to other ANC in Mozambique and sub-Saharan Africa.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4436140/pdf/13012_2015_Article_249.pdf

Trials. 2014 Sep 15;15:359. doi: 10.1186/1745-6215-15-359.

Evaluation of a community health worker intervention and the World Health Organization's Option B versus Option A to improve antenatal care and PMTCT outcomes in Dar es Salaam, Tanzania: study protocol for a cluster-randomized controlled health systems implementation trial.

Sando D, Geldsetzer P, Magesa L, Lema IA, Machumi L, Mwanyika-Sando M, Li N, Spiegelman D, Mungure E, Siril H, Mujinja P, Naburi H, Chalamilla G, Kilewo C, Ekström AM, Fawzi WW, Bärnighausen TW[1].

Department of Global Health and Population, Harvard School of Public Health, Huntington Avenue, Boston, Massachusetts, USA

BACKGROUND:

Mother-to-child transmission of HIV remains an important public health problem in sub-Saharan Africa. As HIV testing and linkage to PMTCT occurs in antenatal care (ANC), major challenges for any PMTCT option in developing countries, including Tanzania, are delays in the first ANC visit and a low overall number of visits. Community health workers (CHWs) have been effective in various settings in increasing the uptake of clinical services and improving treatment retention and adherence. At the beginning of this trial in January 2013, the World Health Organization recommended either of two medication regimens, Option A or B, for prevention of mother-to-child transmission of HIV (PMTCT). It is still largely unclear which option is more effective when implemented in a public healthcare system. This study aims to determine the effectiveness, cost-effectiveness, acceptability, and feasibility of: (1) a community health worker (CWH) intervention and (2) PMTCT Option B in improving ANC and PMTCT outcomes.

METHODS/DESIGN:

This study is a cluster-randomized controlled health systems implementation trial with a two-by-two factorial design. All 60 administrative wards in the Kinondoni and Ilala districts in Dar es Salaam were first randomly allocated to either receiving the CHW intervention or not, and then to receiving either Option B or A. Under the standard of care, facility-based health workers follow up on patients who have missed scheduled appointments for PMTCT, first through a telephone call and then with a home visit. In the wards receiving the CHW intervention, the CHWs: (1) identify pregnant women through home visits and refer them to antenatal care; (2) provide education to pregnant women on antenatal care, PMTCT, birth, and postnatal care; (3) routinely follow up on all pregnant women to ascertain whether they have attended ANC; and (4) follow up on women who have missed ANC or PMTCT appointments.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4247663/pdf/13063_2013_Article_2319.pdf

Trials. 2014 Oct 27;15:417. doi: 10.1186/1745-6215-15-417.

Implementing comprehensive prevention of mother-to-child transmission and HIV prevention for South African couples: study protocol for a randomized controlled trial.

Jones D, Peltzer K[1], Weiss SM, Sifunda S, Dwane N, Ramlagan S, Cook R, Matseke G, Maduna V, Spence A.

HIV/AIDS, STIs and TB (HAST) Research Programme, Human Sciences Research Council (HSRC), Private Bag X41, Pretoria 0001, South Africa

BACKGROUND:

In rural South Africa, only two-thirds of HIV-positive pregnant women seeking antenatal care at community health centers took full advantage of 'prevention of mother-to-child transmission' (PMTCT) services in 2010. Studies generally support male involvement to promote PMTCT, but the nature and impact of that involvement is unclear and untested. Additionally, stigma, disclosure and intimate partner violence pose significant barriers to PMTCT uptake and retention in care, suggesting that male involvement may be 'necessary, but not sufficient' to reduce infant HIV incidence. This study expands on a successful United States President's Emergency Plan for AIDS Relief (PEPFAR)-supported PMTCT couples intervention pilot study conducted in the Mpumalanga province, targeting HIV-positive pregnant women and their partners, the primary objective being to determine whether male partner involvement plus a behavioral intervention will significantly reduce infant HIV incidence.

METHODS/DESIGN:

The study follows a cluster randomized controlled design enrolling two cohorts of HIV-positive pregnant women recruited from 12 randomly assigned Community Health Centers (CHC) (six experimental, six control). The two cohorts will consist of women attending without their male partners (n = 720) and women attending with their male partners (n = 720 couples), in order to determine whether the influence of male participation itself, or combined with a behavioral PMTCT intervention, can significantly reduce infant HIV infection ante-, peri- and postnatally.

DISCUSSION:

It is our intention to significantly increase PMTCT participation from current levels (69%) in the Mpumalanga province to between 90 and 95% through engaging women and couples in a controlled, six session ante- and postnatal risk-reducing and PMTCT promotion intervention addressing barriers to PMTCT (such as stigma, disclosure, intimate partner violence, communication, infant feeding practices and safer conception) that prevent women and men from utilizing treatment opportunities available to them and their infants. Based upon the encouraging preliminary results from our pilot study, successful CHC adoption of the program could have major public health policy implications for containing the epidemic among the most vulnerable populations in rural South Africa: HIV-positive pregnant women and their infants.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4219009/pdf/13063_2014_Article_2273.pdf

AIDS. 2014 Sep 24;28(15):2307-12. doi: 10.1097/QAD.0000000000000409.

Texting improves testing: a randomized trial of two-way SMS to increase postpartum prevention of mother-to-child transmission retention and infant HIV testing.

Odeny TA[1], Bukusi EA, Cohen CR, Yuhas K, Camlin CS, McClelland RS.

Kenya Medical Research Institute (KEMRI), Nairobi, Kenya; Department of Epidemiology cDepartment of Global Health dDepartment of Obstetrics and Gynecology, University of Washington, Seattle, Washington; Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, San Francisco, California; Department of Medicine, University of Washington, Seattle, Washington, USA; Institute of Tropical and Infectious Diseases, University of Nairobi, Nairobi, Kenya.

OBJECTIVE:

Many sub-Saharan African countries report high postpartum loss to follow-up of mother-baby pairs. We aimed to determine whether interactive text messages improved rates of clinic attendance and early infant HIV testing in the Nyanza region of Kenya.

DESIGN:

Parallel-group, unblinded, randomized controlled trial.

METHODS:

HIV-positive pregnant women at least 18 years old and enrolled in the prevention of mother-to-child transmission of HIV programme were randomized to receive either text messages (SMS group, n=195) or usual care (n=193). Messages were developed using formative focus group research informed by constructs of the Health Belief Model. The SMS group received up to eight text messages before delivery (depending on gestational age), and six messages postpartum. Primary outcomes included maternal postpartum clinic attendance and virological infant HIV testing by 8 weeks postpartum. The primary analyses were intention-to-treat.

RESULTS:

Of the 388 enrolled women, 381 (98.2%) had final outcome information. In the SMS group, 38 of 194 (19.6%) women attended a maternal postpartum clinic compared to 22 of 187 (11.8%) in the control group (relative risk 1.66, 95% confidence interval 1.02-2.70). HIV testing within 8 weeks was performed in 172 of 187 (92.0%) infants in the SMS group compared to 154 of 181 (85.1%) in the control group (relative risk 1.08, 95% confidence interval 1.00-1.16).

CONCLUSIONS:

Text messaging significantly improved maternal postpartum visit attendance, but overall return rates for these visits remained low. In contrast, high rates of early infant HIV testing were achieved in both arms, with significantly higher testing rates in the SMS compared to the control infants.

J Acquir Immune Defic Syndr. 2014 Nov 1;67 Suppl 2:S145-9. doi: 10.1097/QAI.0000000000000325.

Cluster randomized trial on the effect of mother support groups on retention-in-care and PMTCT outcomes in Zimbabwe: study design, challenges, and national relevance.

Foster G[1], Kangwende A, Magezi V, Maphosa T, Mashapa R, Mukora-Mutseyekwa F, Mushavi A, Rusakaniko S, Shumba B, Zambezi P.

Ministry of Health and Child Care, Mutare, Zimbabwe; Family AIDS Caring Trust, Mutare, Zimbabwe; Clinical Research Centre, Africa University, Mutare, Zimbabwe; §North West University, Potchefstroom, South Africa; Faculty of Health Sciences, Africa University, Mutare, Zimbabwe; Ministry of Health and Child Care, Harare, Zimbabwe; and #University of Zimbabwe, College of Health Sciences Harare, Zimbabwe.

Abstract

Prevention of mother-to-child transmission (PMTCT) elimination goals are hampered by low rates of retention and antiretroviral treatment adherence. The Eliminating Pediatric AIDS in Zimbabwe (EPAZ) project is assessing whether mother support groups (MSGs) increase rates of retention-in-care of HIV-positive mothers and their exposed infants, increase male participation, and improve other maternal and infant health outcomes. EPAZ is a cluster randomized study involving 30 rural facilities in 2 health districts in Mutare province in eastern Zimbabwe. Facilities were randomly assigned to either the standard-of-care or intervention arms. We established MSGs for HIV-positive mothers at the 15 health facilities in the intervention arm. MSGs met every 2 weeks and were led by an HIV-positive mother who was appointed as MSG coordinator (MSG-C). MSG-Cs contacted nonattending patient-members of support groups by cell phone. If members still do not attend, MSG-Cs inform a health worker who initiates further outreach actions that are standard within the health system. At least 10 HIV-positive mothers are enrolled per facility. Enrollment started in July 2014. The primary outcome measure is retention-in-care of HIV-exposed infants at 12 months of age. Secondary outcome measures are: retention-in-care of HIV-positive mothers at 12 months postpartum, male participation, and other maternal and child health indicators. The study relies on routine health system data supplemented by additional data using tools created for the study. If shown to improve PMTCT retention outcomes, facility-based MSGs have the potential to be scaled up throughout the Zimbabwe National PMTCT program and could be considered in other country programs.

http://www.jaids.org/pt/re/jaids/abstract.00126334-201411011-00008.htm

J Acquir Immune Defic Syndr. 2014 Nov 1;67 Suppl 2:S125-31. doi: 10.1097/QAI.0000000000000320.

Increasing retention in care of HIV-positive women in PMTCT services through continuous quality improvement-breakthrough (CQI-BTS) series in primary and secondary health care facilities in Nigeria: a cluster randomized controlled trial. The Lafiyan Jikin Mata Study.

Oyeledun B[1], Oronsaye F, Oyelade T, Becquet R, Odoh D, Anyaike C, Ogirima F, Ameh B, Ajibola A, Osibo B, Imarhiagbe C, Abutu I; Lafiyan Jikin Mata Study Team.

Center for Integrated Health Programs (CIHP), Abuja, Nigeria; World Health Organization Nigeria (WHO), WHO Country Office, Abuja, Nigeria; INSERM U897, Center de Recherche en Epidémiologie et Biostatistique, Institut de Santé Publique Epidémiologie Développement (ISPED), Université de Bordeaux, Bordeaux, France; and National AIDS and STIs Control Programme (NASCP), Department of Public Health, Federal Ministry of Health, Abuja, Nigeria.

BACKGROUND:

Rates of retention in care of HIV-positive pregnant women in care programs in Nigeria remain generally poor with rates around 40% reported for specific programs. Poor quality of services in health facilities and long waiting times are among the critical factors militating against retention of these women in care. The aim of the interventions in this study is to assess whether a continuous quality improvement intervention using a Breakthrough Series approach in local district hospitals and primary health care clinics will lead to improved retention of HIV-positive women and mothers.

METHODS/DESIGN:

A cluster randomized controlled trial with 32 health facilities randomized to receive a continuous quality improvement/Breakthrough Series intervention or not. The care protocol for HIV-infected pregnant women and mothers is the same in all sites. The quality improvement intervention started 4 months before enrollment of individual HIV-infected pregnant women and initially focused on reducing waiting times for women and also ensuring that antiretroviral drugs are dispensed on the same day as clinic attendance. The primary outcome measure is retention of HIV-positive mothers in care at 6 months postpartum.

DISCUSSION:

Results of this trial will inform whether quality improvement interventions are an effective means of improving retention in prevention of mother-to-child transmission of HIV programs and will also guide where health system interventions should focus to improve the quality of care for HIV-positive women. This will benefit policymakers and program managers as they seek to improve retention rates in HIV care programs.

http://journals.lww.com/jaids/Fulltext/2014/11011/Increasing_Retention_in_Care_of_HIV_Positive_Women.5.aspx

J Acquir Immune Defic Syndr. 2014 Nov 1;67 Suppl 2:S114-9. doi: 10.1097/QAI.0000000000000319.

Improving PMTCT uptake and retention services through novel approaches in peer-based family-supported care in the clinic and community: a 3-arm cluster randomized trial (PURE Malawi).

Rosenberg NE[1], van Lettow M, Tweya H, Kapito-Tembo A, Bourdon CM, Cataldo F, Chiwaula L, Sampathkumar V, Trapence C, Kayoyo V, Kasende F, Kaunda B, Speight C, Schouten E, Eliya M, Hosseinipour M, Phiri S; PURE Malawi Consortium.

University of North Carolina Project, Lilongwe, Malawi; Dignitas International, Zomba, Malawi; Dalla Lana School of Public Health, University of Toronto, Toronto, Canada; Lighthouse Trust, Lilongwe, Malawi; The International Union Against Tuberculosis and Lung Disease, Paris, France; University of Malawi College of Medicine, Blantyre, Malawi; University of Malawi Chancellor College, Zomba, Malawi; Mothers2Mothers, Lilongwe, Malawi; Management Sciences for Health, Lilongwe, Malawi; and Ministry of Health, Lilongwe, Malawi.

Abstract

In July 2011, Malawi introduced an ambitious public health program known as "Option B+," which provides all HIV-infected pregnant and breastfeeding women with lifelong combination

antiretroviral therapy, regardless of clinical stage or CD4 count. Option B+ is expected to have benefits for HIV-infected women, their HIV-exposed infants, and their HIV-uninfected male sex partners. However, these benefits hinge on early uptake of prevention of mother-to-child transmission, good adherence, and long-term retention in care. The Prevention of mother-to-child transmission Uptake and REtention (PURE) study is a 3-arm cluster randomized controlled trial to evaluate whether clinic- or community-based peer support will improve care-seeking and retention in care by HIV-infected pregnant and breastfeeding women, their HIV-exposed infants, and their male sex partners, and ultimately improve health outcomes in all 3 populations. We describe the PURE Malawi Consortium, the initial work conducted to inform the trial and interventions, the trial design, and the analysis plan. We then discuss concerns and expected contributions to Malawi and the region.

http://journals.lww.com/jaids/Fulltext/2014/11011/Improving_PMTCT_Uptake_and_Retention_Services.3.aspx

HIV vaccine

(see Vaccine – HIV vaccine)

Integrated approaches to HIV care and prevention

J Acquir Immune Defic Syndr. 2015 Jun 12. [Epub ahead of print]

The effect of community support agents on retention of people living with HIV in pre-antiretroviral care - A randomized controlled trial in Eastern Uganda.

Muhamadi L[1], Mbona Nazarius T, Daniel K, Gaetano M, Fred WM, Stefan P, Steven James R, Anna Mia E.

District Health Office, Iganga District Administration, Iganga, Uganda; Department of Epidemiology and Biostatistics, Makerere University School of Public Health, Uganda; Department of Public Health Sciences/ Global Health, (IHCAR), Karolinska Institutet, Sweden eDepartment of Health Policy Planning and Management, Makerere University School of Public Health, Kampala, Uganda; IMCH, Department of Women's and Children's Health, Uppsala University, Sweden; Institute of Health Sciences Busoga University, Uganda; Department of Infectious Diseases, Karolinska University Hospital, Sweden; Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD and Johns Hopkins University School of Medicine, Baltimore, MD, United States.

INTRODUCTION:

Over 50% of people living with HIV (PLHIV) in Sub-Saharan Africa are lost to follow-up between diagnosis and initiation of antiretroviral treatment during pre-ARV care. The effect of providing home counselling visits by community support agents on 2-year retention in pre-ARV care was evaluated through a randomized controlled trial in eastern Uganda.

METHODS:

400 newly screened HIV-positive persons were randomly assigned to receive post test counselling alone (routine arm), or post test counselling and monthly home counselling visits by community support agents to encourage them go back for routine pre-ARV care (intervention arm).The outcome measure was the proportion of new PLHIV in either arm who attended their scheduled pre-ARV care visits for at least six out of the anticipated 8 visits in the first 24

months after HIV diagnosis. The difference between the two study arms was assessed using chi-square and T-tests. Mantel-Haenszel Risk Ratios (MHRR) and multivariate logistic models were used to assess the adjusted effect of the intervention on the outcome.

FINDINGS:

In all models generated, participants receiving monthly home counselling visits were 2.5 times more likely to be retained in pre-ARV compared to those in standard care over a period of 24 months (ARR 2.5, 95% CI 2.0-3.0).

INTERPRETATION:

Monthly follow-up home visits by community workers more than doubled the retention of PLHIV in pre-ARV care in rural Uganda and can be applicable in similar resource-poor settings.

FUNDING:

The trial received financial and logistical support in part from Sida and the European Commission through ARVMAC-INCO-DEV FP6 program and also in part (sjr) from the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health. The report has been compiled according to the CONSORT 2012 updated guidelines for reporting parallel group randomized trials and was registered by the current controlled trials CCT as ISRCTN94133652.

PLoS One. 2015 Jun 10;10(6):e0128857. doi: 10.1371/journal.pone.0128857. eCollection 2015.

Characteristics of Women Enrolled into a Randomized Clinical Trial of Dapivirine Vaginal Ring for HIV-1 Prevention.

Palanee-Phillips T[1], Schwartz K[2], Brown ER[3], Govender V[4], Mgodi N[5], Kiweewa FM[6], Nair G[7], Mhlanga F[5], Siva S[4], Bekker LG[8], Jeenarain N[4], Gaffoor Z[4], Martinson F[9], Makanani B[10], Naidoo S[4], Pather A[4], Phillip J[4], Husnik MJ[3], van der Straten A[11], Soto-Torres L[12], Baeten J[13].

Wits Reproductive Health and HIV Research Institute, University of the Witswatersrand, School of Clinical Medicine, Johannesburg, South Africa; FHI 360, Durham, NC, United States of America; Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, HIV Prevention Research Unit, South African Medical Research Council, Durban, South Africa; University of Zimbabwe-University of California San Francisco Collaborative Research Program (UZ-UCSF) Research Collaboration, Harare, Zimbabwe; Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda; Centre for AIDS Programme of Research in SA (CAPRISA), Durban, South Africa; Desmond Tutu HIV Foundation Clinical Research Site, Cape Town, South Africa; UNC Lilongwe Clinical Research Site, Lilongwe, Malawi; College of Medicine-John Hopkins University Research Project Queen Elizabeth Central Hospital, Blantyre, Malawi; RTI International, San Francisco, CA, USA; Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Mental Health, and Eunice Shriver Kennedy, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, United States of America; Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA, United States of America.

INTRODUCTION:

Women in sub-Saharan Africa are a priority population for evaluation of new biomedical HIV-1 prevention strategies. Antiretroviral pre-exposure prophylaxis is a promising prevention approach; however, clinical trials among young women using daily or coitally-dependent products have found low adherence. Antiretroviral-containing vaginal microbicide rings, which release medication over a month or longer, may reduce these adherence challenges.

METHODS:

ASPIRE (A Study to Prevent Infection with a Ring for Extended Use) is a phase III, randomized, double-blind, placebo-controlled trial testing the safety and effectiveness of a vaginal ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine for prevention of HIV-1 infection. We describe the baseline characteristics of African women enrolled in the ASPIRE trial.

RESULTS:

Between August 2012 and June 2014, 5516 women were screened and 2629 HIV-1 seronegative women between 18-45 years of age were enrolled from 15 research sites in Malawi, South Africa, Uganda, and Zimbabwe. The median age was 26 years (IQR 22-31) and the majority (59%) were unmarried. Nearly 100% of participants reported having a primary sex partner in the prior three months but 43% did not know the HIV-1 status of their primary partner; 17% reported additional concurrent partners. Nearly two-thirds (64%) reported having disclosed to primary partners about planned vaginal ring use in the trial. Sexually transmitted infections were prevalent: 12% had Chlamydia trachomatis, 7% Trichomonas vaginalis, 4% Neisseria gonorrhoeae, and 1% syphilis.

CONCLUSIONS:

African HIV-1 seronegative women at risk of HIV -1 infection were successfully enrolled into a phase III trial of dapivirine vaginal ring for HIV-1 prevention.

JAMA. 2014 Jul 23-30;312(4):362-71. doi: 10.1001/jama.2014.8735.

Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial.

Mugo NR[1], Hong T[2], Celum C[3], Donnell D[4], Bukusi EA[5], John-Stewart G[6], Wangisi J[7], Were E[8], Heffron R[2], Matthews LT[9], Morrison S[2], Ngure K[10], Baeten JM[3]; Partners PrEP Study Team.

Department of Global Health, University of Washington, Seattle2Centre for Clinical Research Kenya Medical Research Institute, Nairobi, Kenya3Department of Obstetrics and Gynaecology, Kenyatta National Hospital, Nairobi, Kenya; The AIDS Support Organization (TASO), Kampala, Uganda; Department of Reproductive Health, Moi University, Eldoret, Kenya; Division of Infectious Disease, Massachusetts General Hospital, Boston13Center for Global Health, Massachusetts General Hospital, Boston; Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya.

IMPORTANCE:

Antiretroviral preexposure prophylaxis (PrEP), using tenofovir disoproxil fumarate (TDF) and combination emtricitabine/tenofovir disoproxil fumarate (FTC+TDF), is efficacious for

prevention of human immunodeficiency virus (HIV) acquisition. PrEP could reduce periconception HIV risk, but the effect on pregnancy outcomes is not well defined.

OBJECTIVE:

To assess pregnancy incidence and outcomes among women using PrEP during the periconception period.

DESIGN, SETTING, AND PARTICIPANTS:

Randomized trial among 1785 HIV-serodiscordant heterosexual couples (the Partners PrEP Study) in which the female partner was HIV uninfected that demonstrated that PrEP was efficacious for HIV prevention, conducted between July 2008 and June 2013 at 9 sites in Kenya and Uganda.

INTERVENTIONS:

Daily oral TDF (n = 598), combination FTC+TDF (n = 566), or placebo (n = 621) through July 2011, when PrEP demonstrated efficacy for HIV prevention. Thereafter, participants continued receiving active PrEP without placebo. Pregnancy testing occurred monthly and study medication was discontinued when pregnancy was detected.

MAIN OUTCOMES AND MEASURES:

Pregnancy incidence, birth outcomes (live births, pregnancy loss, preterm birth, congenital anomalies), and infant growth.

RESULTS:

A total of 431 pregnancies occurred. Pregnancy incidence was 10.0 per 100 person-years among women assigned placebo, 11.9 among those assigned TDF (incidence difference, 1.9; 95% CI, -1.1 to 4.9 [P = .22 vs placebo]), and 8.8 among those assigned FTC+TDF (incidence difference, -1.3; 95% CI, -4.1 to 1.5 [P = .39 vs placebo]). Before discontinuation of the placebo treatment group in July 2011, the occurrence of pregnancy loss (96 of 288 pregnancies) was 42.5% for women receiving FTC+TDF compared with 32.3% for those receiving placebo (difference for FTC+TDF vs placebo, 10.2%; 95% CI, -5.3% to 25.7%; P = .16) and was 27.7% for those receiving TDF alone (difference vs placebo, -4.6%; 95% CI, -18.1% to 8.9%; P = .46). After July 2011, the frequency of pregnancy loss (52 of 143 pregnancies) was 37.5% for FTC+TDF and 36.7% for TDF alone (difference, 0.8%; 95% CI, -16.8% to 18.5%; P = .92). Occurrence of preterm birth, congenital anomalies, and growth throughout the first year of life did not differ significantly for infants born to women who received PrEP vs placebo.

CONCLUSIONS AND RELEVANCE:

Among HIV-serodiscordant heterosexual African couples, differences in pregnancy incidence, birth outcomes, and infant growth were not statistically different for women receiving PrEP with TDF alone or combination FTC+TDF compared with placebo at conception. Given that PrEP was discontinued when pregnancy was detected and that CIs for the birth outcomes were wide, definitive statements about the safety of PrEP in the periconception period cannot be made. These results should be discussed with HIV-uninfected women receiving PrEP who are considering becoming pregnant.

Springerplus. 2015 Mar 12;4:122. doi: 10.1186/s40064-015-0886-x. eCollection 2015.

Shamba Maisha: Pilot agricultural intervention for food security and HIV health outcomes in Kenya: design, methods, baseline results and process evaluation of a cluster-randomized controlled trial.

Cohen CR[1], Steinfeld RL[2], Weke E[3], Bukusi EA[3], Hatcher AM[4], Shiboski S[5], Rheingans R[6], Scow KM[7], Butler LM[8], Otieno P[9], Dworkin SL[10], Weiser SD[11].

Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, 550 16th Street, San Francisco, USA ; Center of Expertise in Women's Health & Empowerment, University of California Global Health Institute, San Francisco, CA USA; Centre for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa; Departments of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA USA; Department of Environmental and Global Health, University of Florida, Gainesville, FL USA; Department of Soil Science and Soil Microbial Biology, University of California Davis, Davis, CA USA; Boston Children's Hospital and Harvard Medical School, Boston, MA USA; Centre for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya; Departments of Social and Behavioral Sciences, University of California San Francisco, San Francisco, CA USA ; Center of Expertise in Women's Health & Empowerment, University of California Global Health Institute, San Francisco, CA USA; Departments of Medicine, University of California San Francisco, San Francisco, CA USA ; Center of Expertise in Women's Health & Empowerment, University of California Global Health Institute, San Francisco, CA USA.

BACKGROUND:

Despite advances in treatment of people living with HIV, morbidity and mortality remains unacceptably high in sub-Saharan Africa, largely due to parallel epidemics of poverty and food insecurity.

METHODS/DESIGN:

We conducted a pilot cluster randomized controlled trial (RCT) of a multisectoral agricultural and microfinance intervention (entitled Shamba Maisha) designed to improve food security, household wealth, HIV clinical outcomes and women's empowerment. The intervention was carried out at two HIV clinics in Kenya, one randomized to the intervention arm and one to the control arm. HIV-infected patients >18 years, on antiretroviral therapy, with moderate/severe food insecurity and/or body mass index (BMI) <18.5, and access to land and surface water were eligible for enrollment. The intervention included: 1) a microfinance loan (~$150) to purchase the farming commodities, 2) a micro-irrigation pump, seeds, and fertilizer, and 3) trainings in sustainable agricultural practices and financial literacy. Enrollment of 140 participants took four months, and the screening-to-enrollment ratio was similar between arms. We followed participants for 12 months and conducted structured questionnaires. We also conducted a process evaluation with participants and stakeholders 3-5 months after study start and at study end.

DISCUSSION:

Baseline results revealed that participants at the two sites were similar in age, gender and marital status. A greater proportion of participants at the intervention site had a low BMI in comparison to participants at the control site (18% vs. 7%, p = 0.054). While median CD4 count was similar between arms, a greater proportion of participants enrolled at the intervention arm had a detectable HIV viral load compared with control participants (49% vs. 28%, respectively, p <

0.010). Process evaluation findings suggested that Shamba Maisha had high acceptability in recruitment, delivered strong agricultural and financial training, and led to labor saving due to use of the water pump. Implementation challenges included participant concerns about repaying loans, agricultural challenges due to weather patterns, and a challenging partnership with the microfinance institution. We expect the results from this pilot study to provide useful data on the impacts of livelihood interventions and will help in the design of a definitive cluster RCT.

Lancet Infect Dis. 2014 Jul;14(7):600-8. doi: 10.1016/S1473-3099(14)70741-8. Epub 2014 Jun 2.20

Effect of mobile phone reminders on follow-up medical care of children exposed to or infected with HIV in Cameroon (MORE CARE): a multicentre, single-blind, factorial, randomised controlled trial.

Bigna JJ[1], Noubiap JJ[2], Kouanfack C[3], Plottel CS[4], Koulla-Shiro S[5].

Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon; Faculty of Medicine, University of Montpellier 1, Montpellier, France; Preventing Mother to Child Transmission Unit, Goulfey District Hospital, Goulfey, Cameroon; Internal Medicine Unit, Edéa Regional Hospital, Edéa, Cameroon; Accredited Treatment Centre, Yaoundé Central Hospital, Yaoundé, Cameroon; Department of Medicine, New York University Langone Medical Center, New York, NY, USA

BACKGROUND:

Missed scheduled HIV appointments lead to increased mortality, resistance to antiretroviral therapy, and suboptimum virological response. We aimed to assess whether reminders sent to carers by text message, mobile phone call, or concomitant text message and mobile phone call increase attendance at medical appointments for HIV care in a population of children infected with or exposed to HIV in Cameroon. We also aimed to ascertain the most cost-effective method of mobile-phone-based reminder.

METHODS:

MORE CARE was a multicentre, single-blind, factorial, randomised controlled trial in urban, semi-urban, and rural settings in Cameroon. Carers of children who were infected with or had been exposed to HIV were randomly assigned electronically in blocks of four and allocated (1:1:1:1) sequentially to receive a text message and a call, a text message only, a call only, or no reminder (control). Investigators were masked to group assignment. Text messages were sent and calls made 2 or 3 days before a scheduled follow-up appointment. The primary outcomes were efficacy (the proportion of patients attending a previously scheduled appointment) and efficiency (attendance/[measures of staff working time × cost of the reminders]), as a measure of cost-effectiveness. The primary analysis was by intention to treat. This study is registered with the Pan African Clinical Trials Register, number PACTR201304000528276.

FINDINGS:

The study took place between Jan 28 and May 24, 2013. We randomly assigned 242 adult-child (carer-patient) pairs into four groups: text message plus call (n=61), call (n=60), text message (n=60), and control (n=61). 54 participants (89%) in the text message plus call group, 51 (85%) in the call group, 45 (75%) in the text message group, and 31 (51%) in the control group attended their scheduled appointment. Compared with control, the odds ratios for improvement

in the primary efficacy outcome were 7·5 (95% CI 2·9-19·0; p<0·0001) for text message plus call, 5·5 (2·3-13·1; p=0·0002) for call, and 2·9 (1·3-6·3; p=0·012) for text message. No significant differences were seen in comparisons of the three intervention groups with each other, and there was no synergism between text messages and calls. For the primary efficiency outcome, the mean difference for text message versus text message plus call was 1·5 (95% CI 0·7 to 2·4; p=0·002), for call versus text message plus call was 1·2 (0·7 to 1·6; p<0·0001), and for call versus text message was 0·4 (-1·3 to 0·6; p=0·47).

INTERPRETATION:

Mobile-phone-based reminders of scheduled HIV appointments for carers of paediatric patients in low-resource settings can increase attendance. The most effective method of reminder was text message plus phone call, but text messaging alone was the most efficient (ie, cost-effective) method.

PLoS One. 2015 Jun 10;10(6):e0128857. doi: 10.1371/journal.pone.0128857. eCollection 2015.

Characteristics of Women Enrolled into a Randomized Clinical Trial of Dapivirine Vaginal Ring for HIV-1 Prevention.

Palanee-Phillips T[1], Schwartz K[2], Brown ER[3], Govender V[4], Mgodi N[5], Kiweewa FM[6], Nair G[7], Mhlanga F[5], Siva S[4], Bekker LG[8], Jeenarain N[4], Gaffoor Z[4], Martinson F[9], Makanani B[10], Naidoo S[4], Pather A[4], Phillip J[4], Husnik MJ[3], van der Straten A[11], Soto-Torres L[12], Baeten J[13].

Wits Reproductive Health and HIV Research Institute, University of the Witswatersrand, School of Clinical Medicine, Johannesburg, South Africa; FHI 360, Durham, NC, United States of America; Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, WA, United States of America; HIV Prevention Research Unit, South African Medical Research Council, Durban, South Africa; University of Zimbabwe-University of California San Francisco Collaborative Research Program (UZ-UCSF) Research Collaboration, Harare, Zimbabwe; Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda; Centre for AIDS Programme of Research in SA (CAPRISA), Durban, South Africa; Desmond Tutu HIV Foundation Clinical Research Site, Cape Town, South Africa; UNC Lilongwe Clinical Research Site, Lilongwe, Malawi; College of Medicine-John Hopkins University Research Project Queen Elizabeth Central Hospital, Blantyre, Malawi; RTI International, San Francisco, CA, United States of America; Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Mental Health, and Eunice Shriver Kennedy, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, United States of America; Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA, United States of America.

INTRODUCTION:

Women in sub-Saharan Africa are a priority population for evaluation of new biomedical HIV-1 prevention strategies. Antiretroviral pre-exposure prophylaxis is a promising prevention approach; however, clinical trials among young women using daily or coitally-dependent products have found low adherence. Antiretroviral-containing vaginal microbicide rings, which release medication over a month or longer, may reduce these adherence challenges.

METHODS:

ASPIRE (A Study to Prevent Infection with a Ring for Extended Use) is a phase III, randomized, double-blind, placebo-controlled trial testing the safety and effectiveness of a vaginal ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine for prevention of HIV-1 infection. We describe the baseline characteristics of African women enrolled in the ASPIRE trial.

RESULTS:

Between August 2012 and June 2014, 5516 women were screened and 2629 HIV-1 seronegative women between 18-45 years of age were enrolled from 15 research sites in Malawi, South Africa, Uganda, and Zimbabwe. The median age was 26 years (IQR 22-31) and the majority (59%) were unmarried. Nearly 100% of participants reported having a primary sex partner in the prior three months but 43% did not know the HIV-1 status of their primary partner; 17% reported additional concurrent partners. Nearly two-thirds (64%) reported having disclosed to primary partners about planned vaginal ring use in the trial. Sexually transmitted infections were prevalent: 12% had Chlamydia trachomatis, 7% Trichomonas vaginalis, 4% Neisseria gonorrhoeae, and 1% syphilis.

CONCLUSIONS:

African HIV-1 seronegative women at risk of HIV -1 infection were successfully enrolled into a phase III trial of dapivirine vaginal ring for HIV-1 prevention.

http://www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0128857&representation=PDF

Implement Sci. 2015 Feb 13;10:23. doi: 10.1186/s13012-015-0212-6.

Assisted partner notification services to augment HIV testing and linkage to care in Kenya: study protocol for a cluster randomized trial.

Wamuti BM[1], Erdman LK[2], Cherutich P[3], Golden M[4,5,6], Dunbar M[7], Bukusi D[8], Richardson B[9,10,11], Ng'ang'a A[12], Barnabas R[13,14,15,16], Mutiti PM[17], Macharia P[18], Jerop M[19], Otieno FA[20], Poole D[21], Farquhar C[22,23,24].

Kenyatta National Hospital, Nairobi, Kenya; Department of Pediatrics, University of Toronto, Hospital for Sick Children; Ministry of Health, Government of Kenya, Nairobi, Kenya; Department of Epidemiology, University of Washington; Department of Medicine, University of Washington; Public Health-Seattle & King County HIV/STD Program; Center for Studies in Demography and Ecology, University of Washington; VCT and HIV Prevention Unit, Kenyatta National Hospital; Department of Global Health, University of Washington; Department of Biostatistics, University of Washington; Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, USA; NASCOP, Ministry of Health, Government of Kenya; Department of Epidemiology, University of Washington USA; Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, USA. VCT and HIV Prevention Unit, Kenyatta National Hospital;NASCOP, Ministry of Health, Government of Kenya; Department of Research and Programs, Kenyatta National Hospital Kenya; Department of Research and Programs, Kenyatta National Hospital; Department of Global Health and Population, Harvard University, USA. Department of Epidemiology, University of Washington,

Department of Medicine, University of Washington; Department of Global Health, University of Washington.

Abstract

BACKGROUND:

HIV case-finding and linkage to care are critical for control of HIV transmission. In Kenya, >50% of seropositive individuals are unaware of their status. Assisted partner notification is a public health strategy that provides HIV testing to individuals with sexual exposure to HIV and are at risk of infection and disease. This parallel, cluster-randomized controlled trial will evaluate the effectiveness, cost-effectiveness, and feasibility of implementing HIV assisted partner notification services at HIV testing sites (clusters) in Kenya.

METHODS/DESIGN:

Eighteen sites were selected among health facilities in Kenya with well-established, high-volume HIV testing programs, to reflect diverse communities and health-care settings. Restricted randomization was used to balance site characteristics between study arms (n = 9 per arm). Sixty individuals testing HIV positive ('index partners') will be enrolled per site (inclusion criteria: ≥18 years, positive HIV test at a study site, willing to disclose sexual partners, and never enrolled for HIV care; exclusion criteria: pregnancy or high risk of intimate partner violence). Index partners provide names and contact information for all sexual partners in the past 3 years. At intervention sites, study staff immediately contact sexual partners to notify them of exposure, offer HIV testing, and link to care if HIV seropositive. At control sites, passive partner referral is performed according to national guidelines, and assisted partner notification is delayed by 6 weeks. Primary outcomes, assessed 6 weeks after index partner enrollment and analyzed at the cluster level, are the number of partners accepting HIV testing and number of HIV infections diagnosed and linked to care per index partner. Secondary outcomes are the incremental cost-effectiveness of partner notification and the costs of identifying >1 partner per index case. Participants are closely monitored for adverse outcomes, particularly intimate partner violence. The study is unblinded due to practical limitations.

DISCUSSION:

This rigorously designed trial will inform policy decisions regarding implementation of HIV partner notification services in Kenya, with possible application to other parts of sub-Saharan Africa. Examination of effectiveness and cost-effectiveness in diverse settings will enable targeted application and define best practices.

Helminth and other gastrointestinal disorders

(See also Anaemia, Diarrhoea, Micronutrients and food fortification)

Trans R Soc Trop Med Hyg. 2014 May;108(5):297-304. doi: 10.1093/trstmh/tru037. Epub 2014 Mar 5.

Do shoes reduce hookworm infection in school-aged children on Pemba Island, Zanzibar? A pragmatic trial.

Bird C[1], Ame S, Albonico M, Bickle Q.

Department of Paediatrics, Hillingdon Hospital, Pield Heath Road, Uxbridge UB8 3NN, UK.

BACKGROUND:

A non-blinded, cluster randomised controlled trial to test whether footwear reduces prevalence and intensity of hookworm infection in school-aged children on Pemba Island, Zanzibar.

METHODS:

Six schools were randomised to receive shoes and standard care (deworming with albendazole and health education) and six control schools to receive standard care only. Children provided a stool sample to assess prevalence and intensity of infection with soil transmitted helminthiases (Ascaris lumbricoides, Trichuris trichiura and hookworm). Shoes were then distributed to pupils in the intervention schools; deworming took place as part of the government's mass drug administration programme and a further round of stool samples were collected six months later.

RESULTS:

Nine hundred and fifteen children were traced at follow-up (1056 at baseline). As many children wore shoes in the control arm as the intervention arm. There was no difference in hookworm prevalence (23.4% for intervention schools, 21.3% for control schools, p=0.48), and no difference in mean hookworm infection in eggs/gram of stool (18, 1-36 in intervention schools, 18, 7-29 in control schools, p=0.23). Shoe-wearing increased across all schools, from 47.4 to 82.4%. If a child wore shoes at the end of the study, the relative risk of hookworm infection was 0.7 (CI 0.53-0.91).

CONCLUSION:

Due to contamination, the trial could not conclude that shoes were protective against hookworm infection but the intervention led to behavioural change, and observational data suggest that shoes are protective against hookworm.

Comment
Although published before July 2014, this was one trial missed out from the booklet in 2014

Lancet Infect Dis. 2015 Mar;15(3):277-84. doi: 10.1016/S1473-3099(14)71050-3. Epub 2015 Jan 12.

Efficacy and safety of albendazole plus ivermectin, albendazole plus mebendazole, albendazole plus oxantel pamoate, and mebendazole alone against Trichuris trichiura and concomitant soil-transmitted helminth infections: a four-arm, randomised controlled trial.

Speich B[1], Ali SM[2], Ame SM[2], Bogoch II[3], Alles R[4], Huwyler J[4], Albonico M[5], Hattendorf J[6], Utzinger J[6], Keiser J[7].

Basel, Switzerland

Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, and University of Basel, Basel, Switzerland;Laboratory Division, Public Health Laboratory-Ivo de Carneri,Tanzania;Divisions of Internal Medicine and Infectious Diseases, Toronto General Hospital, Toronto, ON, Canada; Department of Pharmaceutical Sciences, Division of Pharmaceutical Technology, University of Basel, Basel, Switzerland.:Ivo de Carneri Foundation, Milan, Italy;Department of Epidemiology and Public Health, Swiss Tropical and

Public Health Institute, and University of Basel, Basel, Switzerland.;Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, and University of Basel, Basel, Switzerland.

Abstract

BACKGROUND:

Existing anthelmintic drugs (eg, albendazole and mebendazole) have low efficacy against the intestinal nematode species Trichuris trichiura and the drug pipeline is exhausted. We aimed to investigate the strategy of combination chemotherapy with existing drugs to establish whether their efficacy could be enhanced and broadened.

METHODS:

In this randomised controlled trial, we compared three drug combinations and one standard drug alone in children aged 6-14 years in two schools on Pemba Island, Tanzania infected with T trichiura and concomitant intestinal nematodes. We assigned children, via a randomisation list with block sizes of either four or eight, to orally receive albendazole (400 mg) plus ivermectin (200 μg/kg); albendazole (400 mg) plus mebendazole (500 mg); albendazole (400 mg) plus oxantel pamoate (20 mg/kg); or mebendazole (500 mg) alone. The primary endpoints were the proportion of children cured of T trichiura infection and the reduction of T trichiura eggs in stool based on geometric means, both analysed by available case. This study is registered with ISRCTN, number ISRCTN80245406.

FINDINGS:

We randomly assigned 440 eligible children infected with T trichiura between Sept 2, and Oct 18, 2013, to one of the four treatment groups (110 children per group). Data for 431 children were included in the analysis for the primary endpoints. Albendazole plus oxantel pamoate (74 of 108 children cured [68·5%, 95% CI 59·6-77·4]; egg reduction 99·2%, 98·7-99·6) and albendazole plus ivermectin (30 of 109 cured [27·5%, 19·0-36·0]; egg reduction 94·5%, 91·7-96·3) were significantly more effective against T trichiura than mebendazole alone (nine of 107 cured [8·4%, 3·1-13·8]; egg reduction 58·5%, 45·2-70·9). Albendazole plus mebendazole had similar low efficacy (nine of 107 cured [8·4%, 3·1-13·8; egg reduction 51·6%, 35·0-65·3) to mebendazole alone. About a fifth of the children reported adverse events, which were mainly mild. Abdominal cramps and headache were the most common adverse events after treatment; abdominal cramps were reported by 13 (12·0%) children for albendazole plus ivermectin, 10 (9·3%) for albendazole plus mebendazole, 20 (18·2%) for albendazole plus oxantel pamoate, and 16 (14·5%) for mebendazole; headaches were reported by 5 (4·6%) children for albendazole plus ivermectin, 6 (5·6%) for albendazole plus mebendazole, 12 (10·9%) for albendazole plus oxantel pamoate, and 7 (6·4%) for mebendazole.

INTERPRETATION:

Our head-to-head comparison of three combination chemotherapies showed the highest efficacy for albendazole plus oxantel pamoate for the treatment of infection with T trichiura. Further studies should investigate the combination of albendazole plus oxantel pamoate so that it can be considered for soil-transmitted helminthiasis control programmes.

PLoS Negl Trop Dis. 2015 Jun 8;9(6):e0003768. doi: 10.1371/journal.pntd.0003768. eCollection 2015.

Effect of Antihelminthic Treatment on Vaccine Immunogenicity to a Seasonal Influenza Vaccine in Primary School Children in Gabon: A Randomized Placebo-Controlled Trial.

Brückner S[1], Agnandji ST[1], Berberich S[2], Bache E[2], Fernandes JF[2], Schweiger B[3], Massinga Loembe M[2], Engleitner T[4], Lell B[1], Mordmüller B[1], Adegnika AA[5], Yazdanbakhsh M[6], Kremsner PG[1], Esen M[1].

Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany; Centre de Recherches Médicales de Lambaréné, Albert Schweitzer Hospital, Lambaréné, Gabon.;Centre de Recherches Médicales de Lambaréné, Albert Schweitzer Hospital, Lambaréné, Gabon; Nationales Referenzzentrum für Influenza, Robert-Koch-Institut, Berlin, Germany.;Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany;Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany; Centre de Recherches Médicales de Lambaréné, Albert Schweitzer Hospital, Lambaréné, Gabon; Leiden Medical University Center, Department of Parasitology, Leiden, The Netherlands ;Leiden Medical University Center, Department of Parasitology, Leiden, The Netherlands.

BACKGROUND:

Helminth infections are a major public health problem, especially in the tropics. Infected individuals have an altered immune response with evidence that antibody response to vaccination is impaired. Hence, treatment of helminth infections before vaccination may be a simple intervention to improve vaccine immunogenicity. In the present study we investigated whether a single-dose antihelminthic treatment influences antibody responses to a seasonal influenza vaccine in primary school children living in Gabon, Central Africa.

METHODS:

In this placebo-controlled double-blind trial conducted in Gabon the effect of a single-dose antihelminthic treatment with 400 mg albendazole versus a placebo one month prior to immunization with a seasonal influenza vaccine was investigated. Antiviral antibody titers against all three vaccine strains were assessed by haemagglutination inhibition (HI) test at baseline (Day 0; vaccination) and four weeks (Day 28) as well as 12 weeks (Day 84) following vaccination. Vaccine-specific memory B-cell response was measured at Day 0 and Day 84 by vaccine-specific Enzyme-linked Immunospot (ELISpot) assay. The trial is registered with the Pan African Clinical Trials Registry (PACTR) (PACTR201303000434188).

RESULTS:

98 school children aged 6-10 years were randomly allocated to receive either antihelminthic treatment or placebo and were vaccinated one month after the treatment. The prevalence of helminths at baseline was 21%. Vaccine-specific HI titers against at least one of the three vaccine strains increased at Day 28 and Day 84 in all participants. HI titers against both influenza A strains as well as memory B-cell response were modestly higher in the antihelminthic treated group compared to the placebo group but the difference was not statistically significant. Total but not specific IgA was elevated in the antihelminthic treated group compared to the control group at Day 28.

CONCLUSION:

In our setting antihelminthic treatment had no significant effect on influenza vaccine immunogenicity. A trend towards better antiviral and vaccine immunogenicity in the

antihelminthic treated group encourages studies to be conducted with alternative treatment schedules or in populations with a higher helminth burden.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4459874/pdf/pntd.0003768.pdf

Pediatr Allergy Immunol. 2014 Aug;25(5):481-8. doi: 10.1111/pai.12251.

Maternal hookworm modifies risk factors for childhood eczema: results from a birth cohort in Uganda.

Mpairwe H[1], Ndibazza J, Webb EL, Nampijja M, Muhangi L, Apule B, Lule S, Akurut H, Kizito D, Kakande M, Jones FM, Fitzsimmons CM, Muwanga M, Rodrigues LC, Dunne DW, Elliott AM.

MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda.

BACKGROUND:

Worms may protect against allergy. Early-life worm exposure may be critical, but this has not been fully investigated.

OBJECTIVES:

To investigate whether worms in pregnancy and in early childhood are associated with childhood eczema incidence.

METHODS:

The Entebbe Mother and Baby Study, an anthelminthic treatment trial, enrolled pregnant women between 2003 and 2005 in Uganda. Mothers were investigated for worms during pregnancy and children annually. Eczema was doctor-diagnosed from birth to age five years. A planned observational analysis was conducted within the trial cohort to investigate associations between worms and eczema.

RESULTS:

Data for 2345 live-born children were analysed. Hookworm was the most prevalent maternal worm (45%). Childhood worms were less prevalent. Eczema incidence was 4.68/100 person-years. Maternal hookworm was associated with reduced eczema incidence [adjusted hazard ratio (95% confidence interval), p-value: 0.71(0.51-0.99), 0.04] and modified effects of known risk factors for eczema: Dermatophagoides-specific IgE in children was positively associated with eczema incidence if the mother had no hookworm [2.72(1.11-6.63), 0.03], but not if the mother had hookworm [0.41(0.10-1.69), 0.22], interaction p-value = 0.03. Similar interactions were seen for maternal history of eczema {[2.87(1.31-6.27, 0.008) vs. [0.73(0.23-2.30), 0.60], interaction p-value = 0.05}, female gender {[1.82(1.22-2.73), 0.004 vs. [0.96(0.60-1.53), 0.87], interaction p-value = 0.04} and allergen-specific IgE. Childhood Trichuris trichiura and hookworm were inversely associated with eczema.

CONCLUSIONS:

Maternal hookworm modifies effects of known risk factors for eczema. Mechanisms by which early-life worm exposures influence allergy need investigation. Worms or worm products, and intervention during pregnancy have potential for primary prevention of allergy.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4312885/pdf/pai0025-0481.pdf

Parasit Vectors. 2014 Aug 15;7:367. doi: 10.1186/1756-3305-7-367.

Does vitamin A supplementation protect schoolchildren from acquiring soil-transmitted helminthiasis? A randomized controlled trial.

Al-Mekhlafi HM[1], Anuar TS, Al-Zabedi EM, Al-Maktari MT, Mahdy MA, Ahmed A, Sallam AA, Abdullah WA, Moktar N, Surin J.

Department of Parasitology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

BACKGROUND:

Despite the intensive global efforts to control intestinal parasitic infections, the prevalence of soil-transmitted helminth (STH) infections is still very high in many developing countries particularly among children in rural areas.

METHODS:

A randomized, double-blind, placebo-controlled trial was conducted on 250 Aboriginal schoolchildren in Malaysia to investigate the effects of a single high-dose of vitamin A supplementation (200,000 IU) on STH reinfection. The effect of the supplement was assessed at 3 and 6 months after receiving interventions; after a complete 3-day deworming course of 400 mg/daily of albendazole tablets.

RESULTS:

Almost all children (98.6%) were infected with at least one STH species. The overall prevalence of ascariasis, trichuriasis and hookworm infection was 67.8%, 95.5% and 13.4%, respectively. Reinfection rates of Ascaris, Trichuris and hookworm were high; at 6 months, assessment reached 80% of the prevalence reported before treatment. There were no significant differences in the reinfection rates and intensities of STH between vitamin A supplemented-children and those who received placebo at 3 and 6 months ($p > 0.05$).

CONCLUSIONS:

Vitamin A supplementation showed no protective effect against STH reinfection and this could be due to the high endemicity of STH in this community. Long-term interventions to reduce poverty will help significantly in reducing this continuing problem and there is no doubt that reducing intestinal parasitic infection would have a positive impact on the health, nutrition and education of these children.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4141119/pdf/13071_2014_Article_1552.pdf

Injury prevention

Public Health. 2014 Sep;128(9):825-30. doi: 10.1016/j.puhe.2014.06.017. Epub 2014 Sep 2.

Effect of educating mothers on injury prevention among children aged <5 years using the Health Belief Model: a randomized controlled trial.

Cheraghi P[1], Poorolajal J[2], Hazavehi SM[3], Rezapur-Shahkolai F[4].

Department of Public Health, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.;Modelling of Non-communicable Diseases Research Centre, Department of Epidemiology and Biostatistics, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.;Research Centre for Health Sciences and Department of Public Health, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.;Research Centre for Health Sciences and Department of Public Health, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.

OBJECTIVES:

To assess the effect of the Health Belief Model (HBM) on the education of mothers for promoting safety and preventing injury among children aged <5 years.

STUDY DESIGN:

Randomized controlled trial.

METHODS:

This study was conducted in Hamadan City, West Iran in 2012. One hundred and twenty mothers participated in this study, divided into intervention and control groups (60 mothers in each group). The intervention group participated in an educational programme consisting of four 1-hour sessions twice per week. The education programme was based on the HBM. The participants of both groups were evaluated before the intervention and two months after the intervention using a questionnaire. The validity and reliability of the questionnaire were tested with a pilot study. The questionnaire consisted of three parts: demographic characteristics; knowledge, practices and HBM constructs (perceived sensitivity, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy); and history of recent injuries to the child. Student's t-test was used to compare the mean differences, and $P < 0.05$ was considered to indicate significance.

RESULTS:

None of the 120 participants dropped out of the study. The mean differences in knowledge, perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, self-efficacy and practices after the intervention, between the two groups, were 3.98, 3.57, 3.97, 1.57, -7.08, 0.82, 2.95 and 2.47, respectively. All differences were statistically significant ($P = 0.001$).

CONCLUSIONS:

Educational programmes based on the HBM can be used as an effective approach in planning and developing preventive programmes for injury prevention and safety promotion in children aged <5 years.

J Neurosurg Pediatr. 2014 Jul;14(1):94-100. doi: 10.3171/2014.3.PEDS13295. Epub 2014 Apr 25.

How can we teach them about neurotrauma prevention? Prospective and randomized "Pense Bem-Caxias do Sul" study with multiple interventions in preteens and adolescents.

Falavigna A[1], Medeiros GS, Canabarro CT, Barazzetti DO, Marcon G, Carneiro Monteiro GM, Bossardi JB, da Silva PG, Teles AR, Velho MC, Ferrari P.

Department of Neurology and Neurosurgery, University of Caxias do Sul;

OBJECT.: A previous study published by the authors showed that a single intervention could not change the baseline attitudes toward neurotrauma prevention. The present study was designed to evaluate the effectiveness of multiple interventions in modifying knowledge and attitudes for the prevention of neurotrauma in Brazilian preteens and adolescents.

METHODS:

In a randomized controlled trial, fifth-year primary school (PS) and second-year high school (HS) students were divided into a control and 2 intervention (single/multiple) groups. The study was conducted in the following 8 stages: T1, questionnaire to measure baseline characteristics; T2, lecture on trauma prevention; T3, reapplying the questionnaire used in T1; T4, Traffic Department intervention; T5, a play about trauma and its consequences; T6, Fire Department intervention; T7, Emergency Medical Service intervention; and T8, reapplying the questionnaire used in T1 and T3. Positive answers were considered those affirming the use of safety devices "always or sometimes" and negative as "never" using safety devices.

RESULTS:

The sample consisted of 535 students. Regarding attitudes, students in all groups at any stage of measurement showed protective behavior more than 95% of the time about seat belt use. There were only differences between attitudes in PS and HS students on T8 assessment concerning the use of safety equipment on bikes in the multiple-intervention group and concerning the use of safety equipment on skateboards and rollerblades in single- and multiple-intervention groups. These differences were caused mainly by the reduction in positive answers by the HS group, rather than by the increase in positive or protective answers by the PS group. However, there was no difference when the control and intervention groups were compared, independent of the attitudes or the student groups studied. The most important reason for not using protective devices was the belief that they would not get hurt.

CONCLUSIONS:

Multiple and different types of educational interventions, such as lectures, scenes from plays about trauma and its consequences, traffic and fire department intervention, and medical emergency intervention directed to preteens and adolescents from public and private schools did not modify most students' attitudes toward injury prevention. Clinical trial registration no: U1111-1121-0192 (National System of Ethics and Research in Brazil).

Integrated management of Childhood Illness (IMCI)

J Glob Health. 2015 Jun;5(1):010401. doi: 10.7189/jogh.05.010401.

Impact on inequities in health indicators: Effect of implementing the integrated management of neonatal and childhood illness programme in Haryana, India.

Taneja S[1], Bahl S[1], Mazumder S[1], Martines J[2], Bhandari N[1], Bhan MK[3].

Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.;Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway;Ministry of Science and Technology, Government of India, New Delhi, India.

BACKGROUND:

A trial to evaluate the Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy showed that the intervention resulted in lower infant mortality and improved infant care practices. In this paper, we present the results of a secondary analysis to examine the effect of the IMNCI strategy on inequities in health indicators.

METHODS:

The trial was a cluster-randomized controlled trial in 18 primary health centre areas. For this analysis, the population was divided into subgroups by wealth status (using Principal Component Analysis), religion and caste, education of mother and sex of the infant. Multiple linear regression analysis was used to examine inequity gradients in neonatal and post-neonatal mortality, care practices and care seeking, and the differences in these gradients between intervention and control clusters.

FINDINGS:

Inequity in post-neonatal infant mortality by wealth status was lower in the intervention as compared to control clusters (adjusted difference in gradients 2.2 per 1000, 95% confidence interval (CI) 0 to 4.4 per 1000, P = 0.053). The intervention had no effect on inequities in neonatal mortality. The intervention resulted in a larger effect on breastfeeding within one hour of birth in poorer families (difference in inequity gradients 3.0%, CI 1.5 to 4.5, P < 0.001), in lower caste and minorities families, and in infants of mothers with fewer years of schooling. The intervention also reduced gender inequity in care seeking for severe neonatal illness from an appropriate provider (difference in inequity gradients 9.3%, CI 0.4 to 18.2, P = 0.042).

CONCLUSIONS:

Implementation of IMNCI reduced inequities in post-neonatal mortality, and newborn care practices (particularly starting breastfeeding within an hour of birth) and health care-seeking for severe illness. In spite of the intervention substantial inequities remained in the intervention group and therefore further efforts to ensure that health programs reach the vulnerable population subgroups are required.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4306296/pdf/jogh-05-010401.pdf

BMJ. 2014 Aug 29;349:g4988. doi: 10.1136/bmj.g4988.

Effect of implementation of integrated management of neonatal and childhood illness programme on treatment seeking practices for morbidities in infants: cluster randomised trial.

Mazumder S[1], Taneja S[1], Bahl R[2], Mohan P[3], Strand TA[4], Sommerfelt H[5], Kirkwood BR[6], Goyal N[1], Van Den Hombergh H[3], Martines J[5], Bhandari N[7]; Integrated Management of Neonatal and Childhood Illness Evaluation Study Group.\

Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.; Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland.;UNICEF India Country Office, New Delhi, India.;Centre for International Health, University of Bergen, Norway.;Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway.;London School of Hygiene and Tropical Medicine, London, UK.;Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.

OBJECTIVE:

To determine the effect of implementation of the Integrated Management of Neonatal and Childhood Illness strategy on treatment seeking practices and on neonatal and infant morbidity.

DESIGN:

Cluster randomised trial.

SETTING:

Haryana, India.

PARTICIPANTS:

29,667 births in nine intervention clusters and 30,813 births in nine control clusters.

MAIN OUTCOME MEASURES:

The pre-specified outcome was the effect on treatment seeking practices. Post hoc exploratory analyses assessed morbidity, hospital admission, post-neonatal infant care, and nutritional status outcomes.

INTERVENTIONS:

The Integrated Management of Neonatal and Childhood Illness intervention included home visits by community health workers, improved case management of sick children, and strengthening of health systems. Outcomes were ascertained through interviews with randomly selected caregivers: 6204, 3073, and 2045 in intervention clusters and 6163, 3048, and 2017 in control clusters at ages 29 days, 6 months, and 12 months, respectively.

RESULTS:

In the intervention cluster, treatment was sought more often from an appropriate provider for severe neonatal illness (risk ratio 1.76, 95% confidence interval 1.38 to 2.24), for local neonatal infection (4.86, 3.80 to 6.21), and for diarrhoea at 6 months (1.96, 1.38 to 2.79) and 12 months (1.22, 1.06 to 1.42) and pneumonia at 6 months (2.09, 1.31 to 3.33) and 12 months (1.44, 1.00 to 2.08). Intervention mothers reported fewer episodes of severe neonatal illness (risk ratio 0.82, 0.67 to 0.99) and lower prevalence of diarrhoea (0.71, 0.60 to 0.83) and pneumonia (0.73, 0.52 to 1.04) in the two weeks preceding the 6 month interview and of diarrhoea (0.63, 0.49 to 0.80) and pneumonia (0.60, 0.46 to 0.78) in the two weeks preceding the 12 month interview. Infants

in the intervention clusters were more likely to still be exclusively breast fed in the sixth month of life (risk ratio 3.19, 2.67 to 3.81).

CONCLUSION:

Implementation of the Integrated Management of Neonatal and Childhood Illness programme was associated with timely treatment seeking from appropriate providers and reduced morbidity, a likely explanation for the reduction in mortality observed following implementation of the programme in this study.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4148946/pdf/bmj.g4988.pdf

Intravenous fluids

Indian Pediatr. 2014 Dec;51(12):969-74.

Safety and efficacy of isotonic (0.9%) vs. hypotonic (0.18%) saline as maintenance intravenous fluids in children: a randomized controlled trial.

Shamim A[1], Afzal K, Ali SM.

Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. Correspondence to: Dr Ahmar Shamim, Assistant Professor, Mahatma Gandhi Mission Medical College, Navi Mumbai, Maharashtra, India.

OBJECTIVE:

To compare the safety and efficacy of isotonic versus hypotonic maintenance fluid in children.

DESIGN:

Randomized controlled trial.

SETTING:

Tertiary-level teaching hospital.

PARTICIPANTS:

60 children (age 0.5 to 12 years) who were admitted and anticipated to receive intravenous fluid for the next 48 hours.

INTERVENTION:

Hypotonic fluid (Standard maintenance volume as 0.18% NaCl in 5% dextrose) or Isotonic fluid (60% Standard maintenance volume as 0.9% NaCl solution in 5% dextrose).

OUTCOME MEASURES:

Primary: Incidence of hyponatremia. Secondary: Serum sodium, serum osmolality, blood sugar, blood urea, serum creatinine, serum potassium, serum chloride, pH, urine output, change in weight, morbidity and death.

RESULTS:

At 24 hours, hyponatremia was noted in 7 (24%) patients in the isotonic and 16 (55%) in hypotonic group (P=0.031). At 48 hours, hyponatremia was noted in 4 (14%) and 13 (45%) patients in isotonic and hypotonic group, respectively (P=0.02). There was significant change in sodium levels in both isotonic (P=0.036) and hypotonic (P<0.001) intervention groups. The peak fall in mean serum sodium level was noted at 24 hours (-6.5, 95%CI: -3.5, -9.6 mEq/L; P<0.001) in hypotonic group. In isotonic group, there was significant increase between 24 and 48 hours (4.3, 95% CI: 0.1, 8.4 mEq/L; P=0.04).

CONCLUSIONS:

Reduced volume isotonic fluid results in fewer episodes of hyponatremia than hypotonic fluid in sick children during the first 48 hours of intravenous fluid therapy.

Indian J Pediatr. 2015 Jun 2. [Epub ahead of print]

Isotonic versus Hypotonic Parenteral Maintenance Fluids in Very Severe Pneumonia.

Ramanathan S[1], Kumar P, Mishra K, Dutta AK.

Department of Pediatrics, Lady Hardinge Medical College, Kalawati Saran Children's Hospital, New Delhi, India.

OBJECTIVE:

To compare the risk of hyponatremia between hypotonic and isotonic parenteral maintenance solutions (PMS) administered to children with very severe pneumonia, admitted in the general pediatric ward.

METHODS:

A randomized controlled open label trial was conducted in the pediatrics department of a tertiary care medical college hospital including euvolemic children 2 mo to 5 y of age, fulfilling the WHO clinical definition of very severe pneumonia and requiring PMS. They were randomized to receive either isotonic PMS (0.9 % saline in 5 % dextrose and potassium chloride 20 meq/L) or hypotonic PMS (0.18 % saline in 5 % dextrose and potassium chloride 20 meq/L) at standard rates for next 24 h.

RESULTS:

A total of 119 children were randomized (59: Isotonic; 60: Hypototonic PMS). Nine (15 %) children in the isotonic PMS group and 29 (48 %) in the hypotonic PMS group developed hyponatremia during the study period, (p <0.001) with a relative risk being 3.16 (95 % CI 1.64 to 6.09). Mean serum sodium was significantly lower in the hypotonic group compared to the isotonic group (p < 0.001 each at 6, 12 and 24 h). The difference in mean change in serum sodium from baseline was also significant at 12 and 24 h (5.4 and 5.8 meq/L respectively; p < 0.001 each).

CONCLUSIONS:

This study demonstrates the rationality of the use of isotonic PMS in children with respiratory infections, a condition regularly encountered by most pediatricians

Indian J Pediatr. 2015 Jan;82(1):13-8. doi: 10.1007/s12098-014-1436-1. Epub 2014 May 16.

Isotonic intravenous maintenance fluid reduces hospital acquired hyponatremia in young children with central nervous system infections.

Pemde HK[1], Dutta AK, Sodani R, Mishra K.

Department of Pediatrics, Lady Hardinge Medical College, and Kalawati Saran Children's Hospital, New Delhi.

OBJECTIVE:

To find the appropriate type of intravenous fluid (isotonic vs. hypotonic saline in 5 % dextrose) for empiric maintenance fluid therapy in children with central nervous system (CNS) infections that reduces the incidence of hospital acquired hyponatremia.

METHODS:

This blinded randomized controlled trial included hospitalized children aged 3 mo to 5 y with suspected CNS infections requiring intravenous maintenance fluid for at least 24 h. The subjects were randomized to receive 0.9 % saline (Group-A), 0.45 % saline (Group-B) and 0.18 % saline (Group-C) at standard maintenance rate. The outcome measures were proportion of patients developing hyponatremia (serum sodium < 135 mmol/L) after 24 h and serum sodium values at 6, 12, 18, 24 h of receiving maintenance fluids.

RESULTS:

Of the 92 patients enrolled, 31, 30 and 31 patients were randomized to Group A, B and C, respectively. Majority (60.7 %) of the patients in Group-C developed hyponatremia compared with 7.1 % of the children in Group-A and 46.1 % in Group-B. During first 24 h of fluid administration successive fall in the serum sodium values was observed in patients receiving hypotonic fluids. The risk of developing hyponatremia was nearly 6½ (95 % confidence interval (CI) 1.6-26) to 8.5 (95 % CI 2.16-33.39) times more in patients who received hypotonic saline compared to those who received isotonic saline.

CONCLUSIONS:

Administration of 0.9 % saline in 5 % dextrose as intravenous maintenance fluid in children with CNS infection leads to significantly less incidence of hyponatremia when compared to that with hypotonic fluids.

Kidney disease

Kidney Int. 2015 Jan;87(1):217-24. doi: 10.1038/ki.2014.240. Epub 2014 Jul 16.

Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome.

Sinha A[1], Saha A[2], Kumar M[3], Sharma S[1], Afzal K[4], Mehta A[5], Kalaivani M[6], Hari P[1], Bagga A[1].

Division of Nephrology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Ram Manohar Lohia Hospital, New Delhi, India.; Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, New Delhi, India.; Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh, India.; Department of Pediatrics, Sawai Man Singh Medical College, Jaipur, India.;Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India.

Abstract

While studies show that prolonged initial prednisone therapy reduces the frequency of relapses in nephrotic syndrome, they lack power and have risk of bias. In order to examine the effect of prolonged therapy on frequency of relapses, we conducted a blinded, 1:1 randomized, placebo-controlled trial in 5 academic hospitals in India on 181 patients, 1-12 years old, with a first episode of steroid-sensitive nephrotic syndrome. Following 12 weeks of standard therapy, in random order, 92 patients received tapering prednisolone while 89 received matching-placebo on alternate days for the next 12 weeks. On intention-to-treat analyses, primary outcome of number of relapses at 1 year was 1.26 in the 6-month group and 1.54 in the 3-month group (difference -0.28; 95% confidence interval (CI) -0.75, 0.19). Relative relapse rate for 6- vs. 3-month therapy, adjusted for gender, age, and time to initial remission, was 0.70 (95% CI 0.47-1.10). Similar proportions of patients had sustained remission, frequent relapses, and adverse effects due to steroids. Adjusted hazard ratios for first relapse and frequent relapses with prolonged therapy were 0.57 (95% CI, 0.36-1.07) and 1.01 (95% CI, 0.61-1.67), respectively. Thus, extending initial prednisolone treatment from 3 to 6 months does not influence the course of illness in children with nephrotic syndrome. These findings have implications for guiding the duration of therapy of nephrotic syndrome.

Br J Clin Pharmacol. 2015 Feb 11. doi: 10.1111/bcp.12607. [Epub ahead of print]

Population pharmacokinetics of levamisole in children with steroid-sensitive nephrotic syndrome.

Kreeftmeijer-Vegter AR[1,2], Dorlo TP[1,3], Gruppen MP[4], de Boer A[1], de Vries PJ[2,5].

Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, the Netherlands.;ACE Pharmaceuticals BV, the Netherlands.; Department Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.; Department of Paediatric Nephrology, Emma Children's Hospital/Academic Medical Centre, Amsterdam, the Netherlands.; Department of Internal Medicine, Tergooi Ziekenhuis,the Netherlands.

AIM:

The aim was to investigate the population pharmacokinetics of levamisole in children with steroid-sensitive nephrotic syndrome.

METHODS:

Non-linear mixed effects modelling was performed on samples collected during a randomized controlled trial. Samples were collected from children who were receiving 2.5 mg kg^{-1} levamisole (or placebo) orally once every other day. One hundred and thirty-six plasma samples were collected from 38 children from India and Europe and included in the analysis. A one compartment model described the data well.

RESULTS:

The apparent clearance rate (CL/F) and distribution volume (V/F) were 44 l h^{-1} 70 kg^{-1} and 236 l 70 kg^{-1} , respectively; estimated interindividual variability was 32-42%. In addition to allometric scaling of CL/F and V/F to body weight, we identified a significant proportional effect of age on CL/F (-10.1% per year). The pharmacokinetics parameters were not affected by gender, tablet strength or study centre. The median (interquartile range) maximum plasma concentration of levamisole was 438.3 (316.5-621.8) ng ml^{-1} , and the median area under the concentration-time curve was 2847 (2267-3761) ng ml^{-1} h. Median t_{max} and $t_{½}$ values were 1.65 (1.32-2.0) h and 2.60 (2.06-3.65) h, respectively.

CONCLUSIONS:

Here, we present the first pharmacokinetic data regarding levamisole in children with steroid-sensitive nephrotic syndrome. The pharmacokinetic profile of levamisole in children was similar to findings reported in adults, although the elimination rate was slightly higher in children.

http://www.readcube.com/articles/10.1038/ki.2014.240

Leprosy

Lepr Rev. 2014 Dec;85(4):267-74.

Patient profile and treatment satisfaction of Brazilian leprosy patients in a clinical trial of uniform six-month multidrug therapy (U-MDT/CT-BR).

Ferreira IP, Buhrer-Sékula S, De Oliveira MR, Gonçalves Hde S, Pontes MA, Penna ML, Cruz R, Penna GO.

OBJECTIVE:

To describe the profile of patients who participated in the Randomised Clinical Trial for Uniform Multidrug Therapy for Leprosy Patients in Brazil (U-MDT/CT-BR) and determine the level of satisfaction with a uniform therapy regimen, especially among paucibacillary patients.

DESIGN:

This is a descriptive cross-sectional epidemiologic study nested in the wider U-MDT/CT-BR. The study was conducted using a convenience sample composed of patients from the Dona Libânia Dermatology Centre in Fortaleza, Ceará and from the Alfredo da Matta Foundation in Manaus, Amazonas in Brazil. The absolute and relative frequencies of categorical variables and the median age were calculated. Hypothesis testing was done using the Chi-squared and Mann-Whitney tests with a 0.05 level of significance.

RESULTS:

Of the 859 patients included in the clinical trial, 342 were interviewed. The majority of patients were male (58.2%) and multibacillary (78.3%) with a median age of 42 (7-65) years. Most of the interviewees had not completed primary education (48.0%), earned an income below three times the minimum wage (53.8%), were non-smokers (85.1%), did not regularly consume alcohol (88.3%), had not experienced any leprosy-related discrimination (69.2%) and showed a basic knowledge of the disease. With regards to paucibacillary patients, 87.8% and 90.9% of the PB U-MDT and PB R-MDT groups, respectively, indicated that they had not thought of defaulting treatment at any time. On a satisfaction scale of 1-5 (with five as the highest score), 92.7% of PB U-MDT and 100.0% of PB R-MDT patients gave a mark between three and five.

CONCLUSIONS:

The data suggest that the introduction of clofazimine into the therapeutic regimen did not diminish the level of treatment satisfaction among PB patients.

Malaria

(See also Maternal care)

Diagnosis

BMJ. 2015 Mar 4;350:h1019. doi: 10.1136/bmj.h1019.

The impact of providing rapid diagnostic malaria tests on fever management in the private retail sector in Ghana: a cluster randomized trial.

Ansah EK[1], Narh-Bana S[2], Affran-Bonful H[3], Bart-Plange C[4], Cundill B[5], Gyapong M[2], Whitty CJ[5].

Research and Development Division, Ghana Health Service, ; Dodowa Health Research Center, Ghana Health Service.; Dangme West District Health Directorate, Ghana Health Service.;National Malaria Control Programme, Ghana Health Service.;London School of Hygiene & Tropical Medicine, London, UK.

OBJECTIVE:

To examine the impact of providing rapid diagnostic tests for malaria on fever management in private drug retail shops where most poor rural people with fever present, with the aim of reducing current massive overdiagnosis and overtreatment of malaria.

DESIGN:

Cluster randomized trial of 24 clusters of shops.

SETTING:

Dangme West, a poor rural district of Ghana.

PARTICIPANTS:

Shops and their clients, both adults and children.

INTERVENTIONS:

Providing rapid diagnostic tests with realistic training.

MAIN OUTCOME MEASURES:

The primary outcome was the proportion of clients testing negative for malaria by a double-read research blood slide who received an artemisinin combination therapy or other antimalarial. Secondary outcomes were use of antibiotics and antipyretics, and safety.

RESULTS:

Of 4603 clients, 3424 (74.4%) tested negative by double-read research slides. The proportion of slide-negative clients who received any antimalarial was 590/1854 (32%) in the intervention arm and 1378/1570 (88%) in the control arm (adjusted risk ratio 0.41 (95% CI 0.29 to 0.58), P<0.0001). Treatment was in high agreement with rapid diagnostic test result. Of those who were slide-positive, 690/787 (87.8%) in the intervention arm and 347/392 (88.5%) in the control arm received an artemisinin combination therapy (adjusted risk ratio 0.96 (0.84 to 1.09)). There was no evidence of antibiotics being substituted for antimalarials. Overall, 1954/2641 (74%) clients in the intervention arm and 539/1962 (27%) in the control arm received appropriate treatment (adjusted risk ratio 2.39 (1.69 to 3.39), P<0.0001). No safety concerns were identified.

CONCLUSIONS:

Most patients with fever in Africa present to the private sector. In this trial, providing rapid diagnostic tests for malaria in the private drug retail sector significantly reduced dispensing of antimalarials to patients without malaria, did not reduce prescribing of antimalarials to true malaria cases, and appeared safe. Rapid diagnostic tests should be considered for the informal private drug retail sector.Registration Clinicaltrials.gov NCT01907672.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4353311/pdf/bmj.h1019.pdf

J Infect Dis. 2015 Apr 1;211(7):1128-33. doi: 10.1093/infdis/jiu590. Epub 2014 Oct 24.

Plasma concentration of parasite DNA as a measure of disease severity in falciparum malaria.

Imwong M[1], Woodrow CJ[2], Hendriksen IC[2], Veenemans J[3], Verhoef H[4], Faiz MA[5], Mohanty S[6], Mishra S[6], Mtove G[7], Gesase S[8], Seni A[9], Chhaganlal KD[10], Day NP[2], Dondorp AM[2], White NJ[2].

Department of Molecular Tropical Medicine and Genetics.

Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand Centre for Tropical Medicine, Churchill Hospital, University of Oxford; Cell Biology and Immunology Group, Wageningen University Laboratory for Microbiology and Infection Control, Amphia Hospital, Breda, the Netherlands;MRC International Nutrition Group, London School of Hygiene and Tropical Medicine, United Kingdom Cell Biology and Immunology Group, Wageningen University MRC Keneba, the

Gambia.;Dev Care Foundation, Dhaka, Bangladesh.; Department of Medicine, Ispat Hospital, Rourkela, India.;Amani Centre, National Institute for Medical Research, Muheza.; Korogwe Research Laboratory, National Institute for Medical Research, Tanga, Tanzania.; Hospital Central da Beira.; Hospital Central da Beira Faculty of Health Sciences, Catholic University of Mozambique, Beira, Mozambique.

Abstract

In malaria-endemic areas, Plasmodium falciparum parasitemia is common in apparently healthy children and severe malaria is commonly misdiagnosed in patients with incidental parasitemia. We assessed whether the plasma Plasmodium falciparum DNA concentration is a useful datum for distinguishing uncomplicated from severe malaria in African children and Asian adults. P. falciparum DNA concentrations were measured by real-time polymerase chain reaction (PCR) in 224 African children (111 with uncomplicated malaria and 113 with severe malaria) and 211 Asian adults (100 with uncomplicated malaria and 111 with severe malaria) presenting with acute falciparum malaria. The diagnostic accuracy of plasma P. falciparum DNA concentrations in identifying severe malaria was 0.834 for children and 0.788 for adults, similar to that of plasma P. falciparum HRP2 levels and substantially superior to that of parasite densities ($P < .0001$). The diagnostic accuracy of plasma P. falciparum DNA concentrations plus plasma P. falciparum HRP2 concentrations was significantly greater than that of plasma P. falciparum HRP2 concentrations alone (0.904 for children [$P = .004$] and 0.847 for adults [$P = .003$]). Quantitative real-time PCR measurement of parasite DNA in plasma is a useful method for diagnosing severe falciparum malaria on fresh or archived plasma samples.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4354984/pdf/jiu590.pdf

Insecticide-treated bed nets

Malar J. 2014 Jul 7;13:256. doi: 10.1186/1475-2875-13-256.

A phase III trial to evaluate the efficacy, fabric integrity and community acceptance of Netprotect using a recommended long-lasting insecticidal net as positive control.

Van Roey K, Sovannaroth S, Sochantha T, Touch MS, Pigeon O, Sluydts V, Durnez L, Coosemans M[1].

Department of Biomedical Sciences, Institute of Tropical Medicine of Antwerp, Belgium..

BACKGROUND:

The evaluation of new long-lasting insecticidal bed nets (LLINs) is coordinated by the WHO Pesticide Evaluation Scheme (WHOPES). In 2007, Netprotect® was granted WHOPES interim recommendation after Phase I and II evaluations. Present study evaluates Netprotect in a Phase III trial in rural Cambodia.

METHODS:

A randomized, prospective longitudinal study design was used to assess the performance of Netprotect over a period of three years, using conventionally-treated nets and a WHOPES recommended LLIN (PermaNet 2.0) as positive controls. The primary outcomes were the physical integrity, insecticide content and cone bioassay performance using.

RESULTS:

The baseline deltamethrin concentration of 43% of Netprotect nets were below the tolerance limit while 27% of PermaNet 2.0 nets were above the target dose limits. By 36 months Netprotect retained 35% while PermaNet 2.0 retained 49% of baseline insecticide dose. Moreover the proportion of the inactive deltamethrin R-alpha isomer in the Netprotect nets was 33% at the baseline and increased to 69% after three years while it was low and almost constant for PermaNet® 2.0 (3-7%). Only 71% of Netprotect met the WHO criteria for bio-efficacy after three years while at least 80% is required. Moreover Netprotect nets failed for the WHOPES criteria after 12 and 24 months. The reference LLIN met the WHOPES criteria throughout the study. Over the entire three years the reference LLIN did obtain significant higher mosquito mortality than Netprotect. The physical integrity was based on the proportionate hole index and after three years, 25% of Netprotect and 30% of PermaNet 2.0 were in a mediocre or poor state.

CONCLUSION:

Netprotect did not meet the minimum WHO criteria for bio-efficacy after 12, 24 and 36 months. The use of a reference LLIN as positive control was helpful for data interpretation. However, for future three-year studies, it is essential that before initiating any study nets should be checked for their specifications and this for both the candidate LLIN as well as for the reference LLIN. Moreover, to improve the accuracy of the success rate of the candidate LLIN more nets should be tested for their bio-efficacy at the end of the trial.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105388/pdf/1475-2875-13-256.pdf

Malar J. 2014 Dec 8;13:482. doi: 10.1186/1475-2875-13-482.

Strengthening malaria service delivery through supportive supervision and community mobilization in an endemic Indian setting: an evaluation of nested delivery models.

Das A[1], Friedman J, Kandpal E, Ramana GN, Gupta RK, Pradhan MM, Govindaraj R.

Health, Nutrition and Population, The World Bank, Washington, USA.

BACKGROUND:

Malaria continues to be a prominent global public health challenge. This study tested the effectiveness of two service delivery models for reducing the malaria burden, e.g. supportive supervision of community health workers (CHW) and community mobilization in promoting appropriate health-seeking behaviour for febrile illnesses in Odisha, India.

METHODS:

The study population comprised 120 villages from two purposively chosen malaria-endemic districts, with 40 villages randomly assigned to each of the two treatment arms, one with both supportive supervision and community mobilization and one with community mobilization alone, as well as an observational control arm. Outcome measures included changes in the utilization of bed nets and timely care-seeking for fever from a trained provider compared to the control group. Analysis was by intention-to-treat.

RESULTS:

Significant improvements were observed in the reported utilization of bed nets in both intervention arms (84.5% in arm A and 82.4% in arm B versus 78.6% in the control arm; $p < 0.001$). While overall rates of treatment-seeking were equal across study arms, treatment-seeking from a CHW was higher in both intervention arms (28%; $p = 0.005$ and 27.6%; $p = 0.007$) than in the control arm (19.2%). Fever cases were significantly more likely to visit a CHW and receive a timely diagnosis of fever in the combined interventions arm than in the control arm (82.1% vs. 67.1%; $p = 0.025$). Care-seeking from trained providers also increased with a substitution away from untrained providers. Further, fever cases from the combined interventions arm (60.6%; $p = 0.004$) and the community mobilization arm (59.3%; $p = 0.012$) were more likely to have received treatment from a skilled provider within 24 hours than fever cases from the control arm (50.1%). In particular, women from the combined interventions arm were more likely to have received timely treatment from a skilled provider (61.6% vs. 47.2%; $p = 0.028$).

CONCLUSION:

A community-based intervention combining the supportive supervision of community health workers with intensive community mobilization and can be effective in improving care-seeking and preventive behaviour and may be used to strengthen the national malaria control programme.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320454/pdf/12936_2014_Article_3685.pdf

Other preventative interventions

(See also: Vaccines – malaria vaccine)

Cochrane Database Syst Rev. 2015 Jan 13;1:CD010767. doi: 10.1002/14651858.CD010767.pub2.

Intermittent preventive antimalarial treatment for children with anaemia.

Athuman M[1], Kabanywanyi AM, Rohwer AC.

Ifakara Health Institute, Dodoma, Tanzania.

BACKGROUND:

Anaemia is a global public health problem. Children under five years of age living in developing countries (mostly Africa and South-East Asia) are highly affected. Although the causes for anaemia are multifactorial, malaria has been linked to anaemia in children living in malaria-endemic areas. Administering intermittent preventive antimalarial treatment (IPT) to children might reduce anaemia, since it could protect children from new Plasmodium parasite infection (the parasites that cause malaria) and allow their haemoglobin levels to recover.

OBJECTIVES:

To assess the effect of IPT for children with anaemia living in malaria-endemic areas.

SEARCH METHODS:

We searched the Cochrane Infectious Diseases Group Specialized Register, Cochrane Central of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; and LILACS. We also searched the World Health Organization (WHO) International Clinical Trial Registry Platform and metaRegister of Controlled Trials (mRCT) for ongoing trials up to 4 December 2014.

SELECTION CRITERIA:

Randomized controlled trials (RCTs) evaluating the effect of IPT on children with anaemia.

DATA COLLECTION AND ANALYSIS:

Two review authors independently extracted data and assessed risk of bias. We analysed data by conducting meta-analyses, stratifying data according to whether participants received iron supplements or not. We used GRADE to assess the quality of evidence.

MAIN RESULTS:

Six trials with 3847 participants met our inclusion criteria. Trials were conducted in areas of low malaria endemicity (three trials), and moderate to high endemicity (three trials). Four trials were in areas of seasonal malaria transmission. Iron was given to all children in two trials, and evaluated in a factorial design in a further two trials.IPT for children with anaemia probably has little or no effect on the proportion anaemic at 12 weeks follow-up (four trials, 2237 participants, (moderate quality evidence).IPT in anaemic children probably increases the mean change in haemoglobin levels from baseline to follow-up at 12 weeks on average by 0.32 g/dL (MD 0.32, 95% CI 0.19 to 0.45; four trials, 1672 participants, moderate quality evidence); and may improve haemoglobin levels at 12 weeks (MD 0.35, 95% CI 0.06 to 0.64; four trials, 1672 participants, low quality evidence). For both of these outcomes, subgroup analysis did not demonstrate a difference between children receiving iron and those that did not.IPT for children with anaemia probably has little or no effect on mortality or hospital admissions at six months (three trials, 3160 participants moderate quality evidence). Subgroup analysis did not show a difference between those children receiving iron supplements and those that did not.

AUTHORS' CONCLUSIONS:

Trials did show a small effect on average haemoglobin levels but this did not appear to translate into an effect on mortality and hospital admissions. Three of the six trials were conducted in low endemicity areas where transmission is low and thus any protective effect is likely to be modest.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4447115/pdf/CD010767-0001.pdf

Br J Educ Psychol. 2014 Sep;84(Pt 3):483-501. doi: 10.1111/bjep.12033. Epub 2014 Jan 3.

Early childhood malaria prevention and children's patterns of school leaving in the Gambia.

Zuilkowski SS[1], Jukes MC.

Florida State University, Tallahassee, Florida, USA.

BACKGROUND:

Early childhood malaria is often fatal, but its impact on the development and education of survivors has not received much attention. Malaria impacts cognitive development in a number of ways that may impact later educational participation.

AIMS:

In this study, we examine the long-term educational effects of preventing early childhood malaria. Does intermittent preventive treatment (IPT) during early childhood reduce the risk of dropout? If so, does this effect vary by school type - government school versus madrassa?

SAMPLE:

We use data from a 2001 follow-up of a 1985-1987 malaria prevention randomized controlled trial in the Gambia. The sample consists of 562 youth born between 1981 and 1986.

METHODS:

We use discrete-time survival analysis to identify the impact of the intervention on dropout risk over time.

RESULTS:

We find that IPT has a positive impact on dropout for government school students, but not for madrassa attendees. The difference was striking: in government schools, the odds of dropout in the treatment group were one third of those in the control group.

CONCLUSIONS:

Our findings suggest that preventing early childhood malaria may reduce dropout at a relatively low cost. In this intervention, the drugs cost less than one dollar per year per child. While IPT is no longer practised in many countries due to concerns over drug resistance, these results support the conclusion that any type of effective malaria control programme protecting young children, such as consistent and correct use of bed nets, could improve educational attainment in areas where malaria is prevalent.

Lancet. 2015 Apr 11;385(9976):1436-46. doi: 10.1016/S0140-6736(14)61007-2. Epub 2014 Dec 9.

Efficacy of indoor residual spraying with dichlorodiphenyltrichloroethane against malaria in Gambian communities with high usage of long-lasting insecticidal mosquito nets: a cluster-randomised controlled trial.

Pinder M[1], Jawara M[2], Jarju LB[3], Salami K[2], Jeffries D[2], Adiamoh M[2], Bojang K[2], Correa S[2], Kandeh B[3], Kaur H[4], Conway DJ[5], D'Alessandro U[6], Lindsay SW[7].

Medical Research Council Unit, Banjul, The Gambia; London School of Hygiene and Tropical Medicine, London, UK; Durham University, Durham, UK.; Medical Research Council Unit, Banjul, The Gambia.; National Malaria Control Programme, Banjul, The Gambia.; London School of Hygiene and Tropical Medicine, London, UK.; Medical Research Council Unit, Banjul, The Gambia; London School of Hygiene and Tropical Medicine, London, UK.; Medical Research Council Unit, Banjul, The Gambia; Institute of Tropical Medicine, Antwerp, Belgium.; London School of Hygiene and Tropical Medicine, London, UK; Durham University, Durham, UK.

BACKGROUND:

Although many malaria control programmes in sub-Saharan Africa use indoor residual spraying with long-lasting insecticidal nets (LLINs), the two studies assessing the benefit of the combination of these two interventions gave conflicting results. We aimed to assess whether the addition of indoor residual spraying to LLINs provided a significantly different level of protection against clinical malaria in children or against house entry by vector mosquitoes.

METHODS:

In this two-arm cluster, randomised, controlled efficacy trial we randomly allocated clusters of Gambian villages using a computerised algorithm to LLINs alone (n=35) or indoor residual spraying with dichlorodiphenyltrichloroethane plus LLINs (n=35). In each cluster, 65-213 children, aged 6 months to 14 years, were surveyed at the start of the 2010 transmission season and followed in 2010 and 2011 by passive case detection for clinical malaria. Exposure to parasite transmission was assessed by collection of vector mosquitoes with both light and exit traps indoors. Primary endpoints were the incidence of clinical malaria assessed by passive case detection and number of Anopheles gambiae sensu lato mosquitoes collected per light trap per night. Intervention teams had no role in data collection and the data collection teams were not informed of the spray status of villages. The trial is registered at the ISRCTN registry, number ISRCTN01738840.

FINDINGS:

LLIN coverage in 2011 was 3510 (93%) of 3777 children in the indoor residual spraying plus LLIN group and 3622 (95.5%) of 3791 in the LLIN group. In 2010, 7845 children were enrolled, 7829 completed passive case detection, and 7697 (98%) had complete clinical and covariate data. In 2011, 7009 children remained in the study, 648 more were enrolled, 7657 completed passive case detection, and 7545 (98.5%) had complete data. Indoor residual spraying coverage per cluster was more than 80% for both years in the indoor residual spraying plus LLIN group. Incidence of clinical malaria was 0.047 per child-month at risk in the LLIN group and 0.044 per child-month at risk in the indoor residual spraying plus LLIN group in 2010, and 0.032 per child-month at risk in the LLIN group and 0.034 per child-month at risk in the indoor residual spraying plus LLIN group in 2011. The incident rate ratio was 1.08 (95% CI 0.80-1.46) controlling for confounders and cluster by mixed-effect negative binomial regression on all malaria attacks for both years. No significant difference was recorded in the density of vector mosquitoes caught in light traps in houses over the two transmission seasons; the mean number of A gambiae sensu lato mosquitoes per trap per night was 6.7 (4.0-10.1) in the LLIN group and 4.5 (2.4-7.4) in the indoor residual spraying plus LLIN group (p=0.281 in the random-effects linear regression model).

INTERPRETATION:

We identified no significant difference in clinical malaria or vector density between study groups. In this area with high LLIN coverage, moderate seasonal transmission, and susceptible vectors, indoor residual spraying did not provide additional benefit.

Environ Health Perspect. 2015 Apr 10. [Epub ahead of print]

An Assessment of Participatory Integrated Vector Management for Malaria Control in Kenya.

Mutero CM[1], Mbogo C, Mwangangi J, Imbahale S, Kibe L, Orindi B, Girma M, Njui A, Lwande W, Affognon H, Gichuki C, Mukabana WR.

International Centre of Insect Physiology and Ecology, Nairobi, Kenya; and University of Pretoria Centre for Sustainable Malaria Control, School of Health Systems and Public Health, University of Pretoria, Pretoria, South Africa.

BACKGROUND:

The World Health Organization (WHO) recommends integrated vector management (IVM) as a strategy to improve and sustain malaria vector control. However, this approach has not been widely adopted.

OBJECTIVES:

We comprehensively assessed experiences and findings on IVM in Kenya with a view to sharing lessons that might promote its wider application.

METHODS:

The assessment used information from a qualitative external evaluation of two malaria IVM projects implemented between 2006 and 2011 and, an analysis of their accumulated entomological and malaria case data. The project sites were Malindi and Nyabondo, located in coastal and western Kenya respectively. The assessment focused on implementation of five key elements of IVM including integration of vector control methods, evidence-based decision-making, inter-sectoral collaboration, advocacy and social mobilization and, capacity-building.

RESULTS:

IVM was more successfully implemented in Malindi than Nyabondo owing to greater community participation and multi-stakeholder engagement. There was a significant decline in the proportion of malaria cases among children admitted in Malindi Hospital, from 23.7% in 2006 to 10.47% in 2011 ($P<0.001$). However, the projects' operational research methodology did not allow statistical attribution of the decline in malaria and malaria vectors to specific IVM interventions or other factors.

CONCLUSIONS:

Sustaining IVM is likely to require strong participation and support from multiple actors including community-based groups, non-governmental organizations, international and national research institutes and various government ministries. A cluster-randomized controlled trial would be essential to quantify the effectiveness and impact of specific IVM interventions, alone or in combination.

http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2015/4/ehp.1408748.acco.pdf

Malar J. 2014 Aug 16;13:324. doi: 10.1186/1475-2875-13-324.

A cluster-randomized controlled trial to assess the effectiveness of using 15% DEET topical repellent with long-lasting insecticidal nets (LLINs) compared to a placebo lotion on malaria transmission.

Sangoro O[1], Turner E, Simfukwe E, Miller JE, Moore SJ.

Ifakara Health Institute, Tanzania.

BACKGROUND:

Long-lasting insecticidal nets (LLINs) have limited effect on malaria transmitted outside of sleeping hours. Topical repellents have demonstrated reduction in the incidence of malaria transmitted in the early evening. This study assessed whether 15% DEET topical repellent used in combination with LLINs can prevent greater malaria transmission than placebo and LLINs, in rural Tanzania.

METHODS:

A cluster-randomized, placebo-controlled trial was conducted between July 2009 and August 2010 in a rural Tanzanian village. Sample size calculation determined that 10 clusters of 47 households with five people/household were needed to observe a 24% treatment effect at the two-tailed 5% significance level, with 90% power, assuming a baseline malaria incidence of one case/person/year. Ten clusters each were randomly assigned to repellent and control groups by lottery. A total of 4,426 individuals older than six months were enrolled. All households in the village were provided with an LLIN per sleeping space. Repellent and placebo lotion was replaced monthly. The main outcome was rapid diagnostic test (RDT)-confirmed malaria measured by passive case detection (PCD). Incidence rate ratios were estimated from a Poisson model, with adjustment for potential confounders, determined a priori. According-to-protocol approach was used for all primary analyses.

RESULTS:

The placebo group comprised 1972.3 person-years with 68.29 (95% C.I 37.05-99.53) malaria cases/1,000 person-years. The repellent group comprised 1,952.8 person-years with 60.45 (95% C.I 48.30-72.60) cases/1,000 person-years, demonstrating a non-significant 11.44% reduction in malaria incidence rate in this group, (Wilcoxon rank sum z=0.529, p=0.596). Principal components analysis (PCA) of the socio-economic status (SES) of the two groups demonstrated that the control group had a higher SES (Pearson's chi square=13.38, p=0.004).

CONCLUSIONS:

Lack of an intervention effect was likely a result of lack of statistical power, poor capture of malaria events or bias caused by imbalance in the SES of the two groups. Low malaria transmission during the study period could have masked the intervention effect and a larger study size was needed to increase discriminatory power. Alternatively, topical repellents may have no impact on malaria transmission in this scenario. Design and implementation of repellent intervention studies is discussed.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4247706/pdf/12936_2014_Article_3601.pdf

Treatment of uncomplicated malaria

N Engl J Med. 2014 Jul 31;371(5):411-23. doi: 10.1056/NEJMoa1314981.

Spread of artemisinin resistance in Plasmodium falciparum malaria.

Ashley EA[1], Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, Sreng S, Anderson JM, Mao S, Sam B, Sopha C, Chuor CM, Nguon C, Sovannaroth S, Pukrittayakamee S, Jittamala P, Chotivanich K, Chutasmit K, Suchatsoonthorn C, Runcharoen R, Hien TT, Thuy-Nhien NT, Thanh NV, Phu NH, Htut Y, Han KT, Aye KH, Mokuolu OA, Olaosebikan RR, Folaranmi OO, Mayxay M, Khanthavong M, Hongvanthong B, Newton PN, Onyamboko MA, Fanello CI, Tshefu AK, Mishra N, Valecha N, Phyo AP, Nosten F, Yi P, Tripura R, Borrmann S, Bashraheil

M, Peshu J, Faiz MA, Ghose A, Hossain MA, Samad R, Rahman MR, Hasan MM, Islam A, Miotto O, Amato R, MacInnis B, Stalker J, Kwiatkowski DP, Bozdech Z, Jeeyapant A, Cheah PY, Sakulthaew T, Chalk J, Intharabut B, Silamut K, Lee SJ, Vihokhern B, Kunasol C, Imwong M, Tarning J, Taylor WJ, Yeung S, Woodrow CJ, Flegg JA, Das D, Smith J, Venkatesan M, Plowe CV, Stepniewska K, Guerin PJ, Dondorp AM, Day NP, White NJ; Tracking Resistance to Artemisinin Collaboration (TRAC).

BACKGROUND:

Artemisinin resistance in Plasmodium falciparum has emerged in Southeast Asia and now poses a threat to the control and elimination of malaria. Mapping the geographic extent of resistance is essential for planning containment and elimination strategies.

METHODS:

Between May 2011 and April 2013, we enrolled 1241 adults and children with acute, uncomplicated falciparum malaria in an open-label trial at 15 sites in 10 countries (7 in Asia and 3 in Africa). Patients received artesunate, administered orally at a daily dose of either 2 mg per kilogram of body weight per day or 4 mg per kilogram, for 3 days, followed by a standard 3-day course of artemisinin-based combination therapy. Parasite counts in peripheral-blood samples were measured every 6 hours, and the parasite clearance half-lives were determined.

RESULTS:

The median parasite clearance half-lives ranged from 1.9 hours in the Democratic Republic of Congo to 7.0 hours at the Thailand-Cambodia border. Slowly clearing infections (parasite clearance half-life >5 hours), strongly associated with single point mutations in the "propeller" region of the P. falciparum kelch protein gene on chromosome 13 (kelch13), were detected throughout mainland Southeast Asia from southern Vietnam to central Myanmar. The incidence of pretreatment and post-treatment gametocytemia was higher among patients with slow parasite clearance, suggesting greater potential for transmission. In western Cambodia, where artemisinin-based combination therapies are failing, the 6-day course of antimalarial therapy was associated with a cure rate of 97.7% (95% confidence interval, 90.9 to 99.4) at 42 days.

CONCLUSIONS:

Artemisinin resistance to P. falciparum, which is now prevalent across mainland Southeast Asia, is associated with mutations in kelch13. Prolonged courses of artemisinin-based combination therapies are currently efficacious in areas where standard 3-day treatments are failing

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4143591/pdf/emss-59962.pdf

Cochrane Database Syst Rev. 2015 Feb 23;2:CD011547. doi: 10.1002/14651858.CD011547.

Artemisinin-naphthoquine for treating uncomplicated Plasmodium falciparum malaria.

Isba R[1], Zani B, Gathu M, Sinclair D.

Department of Clinical Sciences, Liverpool School of Tropical Medicine,Liverpool, UK,

BACKGROUND:

The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) for treating people with Plasmodium falciparum malaria. Five combinations are currently

recommended, all administered over three days. Artemisinin-naphthoquine is a new combination developed in China, which is being marketed as a one-day treatment. Although shorter treatment courses may improve adherence, the WHO recommends at least three days of the short-acting artemisinin component to eliminate 90% P. falciparum parasites in the bloodstream, before leaving the longer-acting partner drug to clear the remaining parasites.

OBJECTIVES:

To evaluate the efficacy and safety of the artemisinin-naphthoquine combination for treating adults and children with uncomplicated P. falciparum malaria.

SEARCH METHODS:

We searched the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library; MEDLINE; EMBASE; and LILACS up to January 2015. We also searched the metaRegister of Controlled Trials (mRCT) using 'malaria' and 'arte* OR dihydroarte*' as search terms.

SELECTION CRITERIA:

Randomized controlled trials comparing artemisinin-naphthoquine combinations with established WHO-recommended ACTs for the treatment of adults and children with uncomplicated malaria due to P. falciparum.

DATA COLLECTION AND ANALYSIS:

Two review authors independently assessed trials for eligibility and risk of bias, and extracted data. We analysed primary outcomes in line with the WHO 'Protocol for assessing and monitoring antimalarial drug efficacy' and compared drugs using risk ratios (RR) and 95% confidence intervals (CI). Secondary outcomes were effects on gametocytes, haemoglobin, and adverse events. We assessed the quality of evidence using the GRADE approach.

MAIN RESULTS:

Four trials, enrolling 740 adults and children, met the inclusion criteria. Artemisinin-naphthoquine was administered as a single dose (two trials), as two doses given eight hours apart (one trial), and once daily for three days (one trial), and compared to three-day regimens of established ACTs. Three additional small pharmaceutical company trials have been carried out. We have requested the data but have not received a response from the company. Artemisinin-naphthoquine versus artemether-lumefantrineIn three small trials from Benin, Côte d'Ivoire, and Papua New Guinea, both combinations had a very low incidence of treatment failure at Day 28, and there were no differences demonstrated in PCR-unadjusted, or PCR-adjusted treatment failure (three trials, 487 participants, low quality evidence). Only the single study from Papua New Guinea followed participants up to Day 42, and the number of treatment failures remained very low with both combinations (one trial, 186 participants, very low quality evidence). Artemisinin-naphthoquine versus dihydroartemisinin-piperaquineIn a single small trial from Indonesia, treatment failure at Day 28 and Day 42 was very low in both groups with no differences demonstrated (one trial, 144 participants, very low quality evidence).

AUTHORS' CONCLUSIONS:

The results of these few trials of artemisinin-naphthoquine are promising, but further trials from multiple settings are required to reliably demonstrate the relative efficacy and safety compared to established ACTs. Future trials should be adequately powered to demonstrate non-inferiority, and regimens incorporating three days of the artemisinin component are probably preferable to the one-day regimens.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4453860/pdf/CD011547-0001.pdf

J Infect Dis. 2014 Aug 15;210(4):585-92. doi: 10.1093/infdis/jiu171. Epub 2014 Mar 20.

Chloroquine-azithromycin combination antimalarial treatment decreases risk of respiratory- and gastrointestinal-tract infections in Malawian children.

Gilliams EA[1], Jumare J[2], Claassen CW[3], Thesing PC[4], Nyirenda OM[4], Dzinjalamala FK[5], Taylor T[6], Plowe CV[3], Tracy LA[2], Laufer MK[3].

Department of Epidemiology and Public Health, University of Maryland School of Medicine Howard Hughes Medical Institute/Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland.; Department of Epidemiology and Public Health, University of Maryland School of Medicine.; Howard Hughes Medical Institute/Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland.; Blantyre Malaria Project, University of Malawi College of Medicine.; Department of Pharmacy, University of Malawi College of Medicine, Blantyre, Malawi.; Blantyre Malaria Project, University of Malawi College of Medicine Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, E. Lansing, Michigan.

BACKGROUND:

Chloroquine-azithromycin is being evaluated as combination therapy for malaria. It may provide added benefit in treating or preventing bacterial infections that occur in children with malaria.

OBJECTIVE:

We aim to evaluate the effect of treating clinical malaria with chloroquine-azithromycin on the incidence of respiratory-tract and gastrointestinal-tract infections compared to treatment with chloroquine monotherapy.

METHODS:

We compared the incidence density and time to first events of respiratory-tract and gastrointestinal-tract infections among children assigned to receive chloroquine-azithromycin or chloroquine for all symptomatic malaria episodes over the course of 1 year in a randomized longitudinal trial in Blantyre, Malawi.

RESULTS:

The incidence density ratios of total respiratory-tract infections and gastrointestinal-tract infections comparing chloroquine-azithromycin to chloroquine monotherapy were 0.67 (95% confidence interval [CI], .48, .94) and 0.74 (95% CI, .55, .99), respectively. The time to first lower-respiratory-tract and gastrointestinal-tract infections were significantly longer in the chloroquine-azithromycin arm compared to the chloroquine arm (P = .04 and P = .02, respectively).

CONCLUSIONS:

Children treated routinely with chloroquine-azithromycin had fewer respiratory and gastrointestinal-tract infections than those treated with chloroquine alone. This antimalarial combination has the potential to reduce the burden of bacterial infections among children in malaria-endemic countries.

KEYWORDS:

Malawi; azithromycin; chloroquine; gastrointestinal tract infection; malaria treatment; respiratory tract infection; secondary benefit

J Infect Dis. 2014 Dec 15;210(12):1962-71. doi: 10.1093/infdis/jiu341. Epub 2014 Jun 18.

Randomized trial of artesunate-amodiaquine, atovaquone-proguanil, and artesunate-atovaquone-proguanil for the treatment of uncomplicated falciparum malaria in children.

Tahar R[1], Almelli T[2], Debue C[2], Foumane Ngane V[3], Djaman Allico J[4], Whegang Youdom S[3], Basco LK[5].

Unité Mixte de Recherche 216 Mère et Enfant Face aux Infections Tropicales, Institut de Recherche pour le Développement (IRD), Unité de formation et de recherche de Pharmacie, Paris Laboratoire de Recherche sur le Paludisme, Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale, Yaoundé, Cameroon.; Laboratoire de recherche sur le Paludisme, Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale, Yaoundé, Cameroon.; Unité de Recherche Neurobiologie et Développement, Unité Propre de Recherche 3294, Centre National de la Recherche Scientifique, Université Paris-Sud XI, Orsay Laboratoire de Pharmacodynamie Biochimique, Unité de Formation et de Recherche Biosciences, Université de Cocody Département de Biochimie, Institut Pasteur de Côte d'Ivoire, Abidjan, Côte d'Ivoire.

BACKGROUND:

Artemisinin-based combination therapies (ACTs) are recommended for the treatment of acute uncomplicated falciparum malaria in many malaria-endemic countries. Despite the emergence of artemisinin resistance, few alternative non-ACTs, including atovaquone-proguanil, are currently available.

METHODS:

Plasmodium falciparum-infected Cameroonian children ≤5 years old (n = 338) were randomly assigned to artesunate-amodiaquine, atovaquone-proguanil, or artesunate-atovaquone-proguanil treatment groups and followed for 28 days, according to the standard World Health Organization protocol. In vitro response to atovaquone and cytochrome b sequence of clinical isolates were determined.

RESULTS:

Eight late failures and 16 failures (8 late and 8 early failures) were observed after artesunate-amodiaquine and atovaquone-proguanil therapies, respectively. Most late failures were due to reinfections. Artesunate-atovaquone-proguanil was not associated with any failure. After correction by genotyping, per-protocol analysis showed no difference in the efficacy of 3 drugs. However, the proportion of atovaquone-proguanil-treated patients with positive smears on day 3 was much higher (36.0%; P < .05) than that of the artesunate-amodiaquine (2.9%) and

artesunate-atovaquone-proguanil (1.0%) groups. In vitro response and cytochrome b sequence did not indicate atovaquone resistance.

CONCLUSIONS:

Atovaquone-proguanil was characterized by a slow blood schizontocidal action and resulted in early treatment failure in a few patients. Artesunate-atovaquone-proguanil was a highly effective alternative treatment.

Clin Infect Dis. 2014 Aug 15;59(4):509-16. doi: 10.1093/cid/ciu353. Epub 2014 May 13.

Longitudinal outcomes in a cohort of Ugandan children randomized to artemether-lumefantrine versus dihydroartemisinin-piperaquine for the treatment of malaria.

Wanzira H[1], Kakuru A[1], Arinaitwe E[1], Bigira V[1], Muhindo MK[1], Conrad M[2], Rosenthal PJ[2], Kamya MR[3], Tappero JW[4], Dorsey G[2].

Infectious Diseases Research Collaboration, Kampala, Uganda; Department of Medicine, University of California, San Francisco.; Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda.; Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia.

BACKGROUND:

Artemisinin-based combination therapy (ACT) has become the standard of care for the treatment of uncomplicated Plasmodium falciparum malaria. Although several ACT regimens are approved, data guiding optimal choices of ACTs are limited. We compared short- and long-term outcomes in a cohort of young Ugandan children randomized to 2 leading ACTs.

METHODS:

Overall, 312 children were randomized to artemether-lumefantrine or dihydroartemisinin-piperaquine (DP) at the time of the first episode of uncomplicated malaria (median age, 10.5 months). The same treatment was given for all subsequent episodes of uncomplicated malaria and children were followed until they reached 5 years of age. The cohort included a subgroup that was human immunodeficiency virus (HIV) infected (n = 44) or HIV exposed (n = 175) and prescribed trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis. Outcomes included time to recurrent malaria following individual treatments and the overall incidences of treatments for malaria, complicated malaria, and hospitalizations.

RESULTS:

Among children not prescribed TMP-SMX prophylaxis, 4443 treatments for malaria were given over 790 person-years following randomization. Treatment with DP was associated with a lower hazard of recurrent malaria over the 84 days after treatment (hazard ratio, 0.66; 95% confidence interval [CI], .61-.70; P < .001). Children randomized to DP had a lower incidence of all treatments for malaria (incidence rate ratio [IRR], 0.85; 95% CI, .75-.96; P = .01), complicated malaria (IRR, 0.12; 95% CI, .04-.39; P < .001), and hospitalizations (IRR, 0.31; 95% CI, .13-.77; P = .01). Among children prescribed TMP-SMX prophylaxis, there were no significant differences in longitudinal outcomes.

CONCLUSIONS:

Compared to artemether-lumefantrine, the use of DP to treat uncomplicated malaria delayed the time to recurrent malaria and reduced the incidences of treatments for malaria, complicated malaria, and hospitalizations.

Am J Trop Med Hyg. 2014 Nov;91(5):925-35. doi: 10.4269/ajtmh.13-0248. Epub 2014 Sep 22.

Efficacy of artemisinin-based combination treatments of uncomplicated falciparum malaria in under-five-year-old Nigerian children.

Oguche S[1], Okafor HU[1], Watila I[1], Meremikwu M[1], Agomo P[1], Ogala W[1], Agomo C[1], Ntadom G[1], Banjo O[1], Okuboyejo T[1], Ogunrinde G[1], Odey F[1], Aina O[1], Sofola T[1], Sowunmi A[2].

Antimalarial Therapeutic Efficacy Monitoring Group, The Federal Ministry of Health, Abuja, Nigeria.

Abstract

The efficacy of 3-day regimens of artemether-lumefantrine and artesunate-amodiaquine were evaluated in 747 children < 5 years of age with uncomplicated malaria from six geographical areas of Nigeria. Fever clearance was significantly faster (P = 0.006) and the proportion of children with parasitemia 1 day after treatment began was significantly lower (P = 0.016) in artesunate-amodiaquine-compared with artemether-lumefantrine-treated children. Parasite clearance times were similar with both treatments. Overall efficacy was 96.3% (95% confidence interval [CI] 94.5-97.6%), and was similar for both regimens. Polymerase chain reaction-corrected parasitologic cure rates on Day 28 were 96.9% (95% CI 93.9-98.2%) and 98.3% (95% CI 96.1-99.3%) for artemether-lumefantrine and artesunate-amodiaquine, respectively. Gametocyte carriage post treatment was significantly lower than pretreatment (P < 0.0001). In anemic children, mean time to recovery from anemia was 10 days (95% CI 9.04-10.9) and was similar for both regimens. Both treatments were well tolerated and are safe and efficacious treatments of uncomplicated falciparum malaria in young Nigerian children.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4228889/pdf/tropmed-91-925.pdf

J Infect Dis. 2015 Mar 1;211(5):689-97. doi: 10.1093/infdis/jiu540. Epub 2014 Sep 28.

Efficacy and safety of triple combination therapy with artesunate-amodiaquine-methylene blue for falciparum malaria in children: a randomized controlled trial in Burkina Faso.

Coulibaly B[1], Pritsch M[2], Bountogo M[1], Meissner PE[3], Nebié E[1], Klose C[4], Kieser M[4], Berens-Riha N[5], Wieser A[2], Sirima SB[6], Breitkreutz J[7], Schirmer RH[8], Sié A[1], Mockenhaupt FP[9], Drakeley C[10], Bousema T[11], Müller O[12].

Centre de Recherche en Santé de Nouna, Nouna.; Division of Infectious Diseases and Tropical Medicine, Medical Center Department of Bacteriology, Max von Pettenkofer-Institute, Ludwig Maximilian University of Munich German Center for Infection Research, Partner Site Munich.; Department of Pediatrics and Adolescent Medicine, Medical School, Ulm University.; Institute of Medical Biometry and Informatics.; Division of Infectious Diseases and Tropical Medicine,

Medical Center.; Centre de Recherche et de la Formation au Paludisme, Ouagadougou, Burkina Faso.; Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University Düsseldorf.; Biochemistry Centre, Ruprecht-Karls-University, Heidelberg.; Institute of Tropical Medicine and International Health, Charité-Universitätsmedizin Berlin, Germany.; Department of Immunology & Infection, London School of Tropical Medicine and Hygiene, United Kingdom.; Department of Immunology & Infection, London School of Tropical Medicine and Hygiene, United Kingdom Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, the Netherlands.; Institute of Public Health, Medical School.

BACKGROUND:

Methylene blue (MB) has been shown to be safe and effective against falciparum malaria in Africa and to have pronounced gametocytocidal properties.

METHODS:

Three days of treatment with artesunate (AS)-amodiaquine (AQ) combined with MB was compared with AS-AQ treatment in a randomized controlled phase IIb study; the study included 221 children aged 6-59 months with uncomplicated falciparum malaria in Burkina Faso. The primary end point was gametocyte prevalence during follow-up, as determined by microscopy and real-time quantitative nucleic acid sequence-based amplification (QT-NASBA).

RESULTS:

The gametocyte prevalence of Plasmodium falciparum at baseline was 3.6% (microscopy) and 97% (QT-NASBA). It was significantly lower in the AS-AQ-MB than in the AS-AQ group on day 7 of follow-up (microscopy, 1.2% vs 8.9% [P < .05]; QT-NASBA, 36.7% vs 63.3% [P < .001]). Hemoglobin values were significantly lower in the AS-AQ-MB group than in the AS-AQ group at days 2 and 7 of follow-up. Vomiting of the study medication occurred significantly more frequently in the AS-AQ-MB group.

CONCLUSIONS:

The combination of MB with an artemisinin-based combination therapy has been confirmed to be effective against the gametocytes of P. falciparum. MB-based combinations need to be compared with primaquine-based combinations, preferably using MB in an improved pediatric formulation.

Malar J. 2014 Jul 9;13:265. doi: 10.1186/1475-2875-13-265.

Longitudinal study on Plasmodium falciparum gametocyte carriage following artemether-lumefantrine administration in a cohort of children aged 12-47 months living in Western Kenya, a high transmission area.

Andagalu B, Mativo J, Kamau E[1], Ogutu B.

Department of Emerging Infectious Diseases-Global Emerging Infections Surveillance and Response System (DEID-GEIS) Program, United States Army Medical Research Unit-Kenya (USAMRU-K), Kenya Medical Research Institute (KEMRI)-Walter Reed Project.

BACKGROUND:

The effects that artemether-lumefantrine (AL) has on gametocyte dynamics in the short-term have recently been described. However there is limited long-term longitudinal data on the effect of AL on gametocyte dynamics in asymptomatic children.

METHODS:

An epidemiological study was conducted in Kombewa, Western Kenya, in which 270 asymptomatic children aged between 12 and 47 months were enrolled. The subjects were randomized to receive either a course of AL or placebo at enrolment. Active follow-up was conducted for one year.

RESULTS:

The gametocyte prevalence and density dynamics throughout the study period mirrored that of the asexual forms. The proportion of initially parasitaemic subjects becoming gametocytaemic was significantly lower in the AL arm for the first 12 weeks following randomization. The geometric mean gametocyte density was lower in the AL arm for 2 weeks following randomization. None of the variables of interest had a statistically significant effect on the duration of gametocytaemia. There is no effect seen in subjects who are not parasitaemic at the time of drug administration.

CONCLUSIONS:

The treatment of asymptomatic parasitaemic subjects with AL results in a significant reduction in the proportion of subjects who become gametocytaemic for at least 12 weeks.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105514/pdf/1475-2875-13-265.pdf

Antimicrob Agents Chemother. 2014 Oct;58(10):5784-94. doi: 10.1128/AAC.03314-14. Epub 2014 Jul 21.

Effect of coadministered fat on the tolerability, safety, and pharmacokinetic properties of dihydroartemisinin-piperaquine in Papua New Guinean children with uncomplicated malaria.

Moore BR[1], Benjamin JM[2], Salman S[3], Griffin S[2], Ginny E[2], Page-Sharp M[4], Robinson LJ[5], Siba P[6], Batty KT[4], Mueller I[7], Davis TM[8].

School of Medicine and Pharmacology, The University of Western Australia, Crawley, Western Australia, Australia Papua New Guinea Institute of Medical Research, Madang, Madang Province, Papua New Guinea.; Papua New Guinea Institute of Medical Research, Madang, Madang Province, Papua New Guinea.; School of Medicine and Pharmacology, The University of Western Australia, Crawley, Western Australia, Australia.; School of Pharmacy, Curtin University of Technology, Bentley, Western Australia, Australia.; Papua New Guinea Institute of Medical Research, Madang, Madang Province, Papua New Guinea Infection and Immunity, Walter and Eliza Hall Institute, Melbourne, Victoria, Australia Department of Medical Biology, University of Melbourne, Melbourne, Victoria, Australia.; Papua New Guinea Institute of Medical Research, Goroka, Eastern Highlands Province, Papua New Guinea.; Infection and Immunity, Walter and Eliza Hall Institute, Melbourne, Victoria, Australia Department of Medical Biology, University of Melbourne, Melbourne, Victoria, Australia Center de Recerca

en Salut Internacional de Barcelona (CRESIB), Barcelona, Spain.; School of Medicine and Pharmacology, The University of Western Australia, Crawley, Western Australia, Australia

Abstract

Coadministration of dihydroartemisinin-piperaquine (DHA-PQ) with fat may improve bioavailability and antimalarial efficacy, but it might also increase toxicity. There have been no studies of these potential effects in the pediatric age group. The tolerability, safety, efficacy, and pharmacokinetics of DHA-PQ administered with or without 8.5 g fat were investigated in 30 Papua New Guinean children aged 5 to 10 years diagnosed with uncomplicated falciparum malaria. Three daily 2.5:11.5-mg-base/kg doses were given with water (n = 14, group A) or milk (n = 16, group B), with regular clinical/laboratory assessment and blood sampling over 42 days. Plasma PQ was assayed by high-performance liquid chromatography with UV detection, and DHA was assayed using liquid chromatography-mass spectrometry. Compartmental pharmacokinetic models for PQ and DHA were developed using a population-based approach. DHA-PQ was generally well tolerated, and initial fever and parasite clearance were prompt. There were no differences in the areas under the concentration-time curve (AUC0-∞) for PQ (median, 41,906 versus 36,752 μg · h/liter in groups A and B, respectively; P = 0.24) or DHA (4,047 versus 4,190 μg · h/liter; P = 0.67). There were also no significant between-group differences in prolongation of the corrected electrocardiographic QT interval (QTc) initially during follow-up, but the QTc tended to be higher in group B children at 24 h (mean ± standard deviation [SD], 15 ± 10 versus 6 ± 15 ms(0.5) in group A, P = 0.067) and 168 h (10 ± 18 versus 1 ± 23 ms(0.5), P = 0.24) when plasma PQ concentrations were relatively low. A small amount of fat does not change the bioavailability of DHA-PQ in children, but a delayed persistent effect on ventricular repolarization cannot be excluded.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105514/pdf/1475-2875-13-265.pdf

Malar J. 2014 Sep 19;13:369. doi: 10.1186/1475-2875-13-369.

A randomized trial of artesunate-amodiaquine versus artemether-lumefantrine in Ghanaian paediatric sickle cell and non-sickle cell disease patients with acute uncomplicated malaria.

Adjei GO[1], Goka BQ, Enweronu-Laryea CC, Rodrigues OP, Renner L, Sulley AM, Alifrangis M, Khalil I, Kurtzhals JA.

Centre for Tropical Clinical Pharmacology and Therapeutics, University of Ghana Medical School, College of Health Sciences.

BACKGROUND:

Sickle cell disease (SCD) is a genetic disorder common in malaria endemic areas. In endemic areas, malaria is a major cause of morbidity and mortality among SCD patients. This suggests the need for prompt initiation of efficacious anti-malarial therapy in SCD patients with acute malaria. However, there is no information to date, on the efficacy or safety of artemisinin combination therapy when used for malaria treatment in SCD patients.

METHODS:

Children with SCD and acute uncomplicated malaria (n=60) were randomized to treatment with artesunate-amodiaquine (AA), or artemether-lumefantrine (AL). A comparison group of non-

SCD children (HbAA genotype; n=59) with uncomplicated malaria were also randomized to treatment with AA or AL. Recruited children were followed up and selected investigations were done on days 1, 2, 3, 7, 14, 28, 35, and 42. Selected clinical and laboratory parameters of the SCD patients were also compared with a group of malaria-negative SCD children (n=82) in steady state.

RESULTS:

The parasite densities on admission were significantly lower in the SCD group, compared with the non-SCD group (p=0.0006). The parasite reduction ratio (PRR) was lower, clearance was slower (p<0.0001), and time for initial parasitaemia to decline by 50 and 90% were longer for the SCD group. Adequate clinical and parasitological response (ACPR) on day 28 was 98.3% (58/59) in the SCD group and 100% (57/57) in the non-SCD group. Corresponding ACPR rates on day 42 were 96.5% (55/57) in the SCD group and 96.4% (53/55) in the non-SCD group. The fractional changes in haemoglobin, platelets and white blood cell counts between baseline (day 0) and endpoint (day 42) were 16.9, 40.6 and 92.3%, respectively, for the SCD group, and, 12.3, 48.8 and 7.5%, respectively, for the non-SCD group. There were no differences in these indices between AA- and AL-treated subjects.

CONCLUSIONS:

The parasite clearance of SCD children with uncomplicated malaria was slower compared with non-SCD children. AA and AL showed similar clinical and parasitological effects in the SCD and non-SCD groups. The alterations in WBC and platelet counts may have implications for SCD severity.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176868/pdf/12936_2014_Article_3400.pdf

Value Health. 2014 Dec;17(8):783-91. doi: 10.1016/j.jval.2014.07.010. Epub 2014 Oct 7.

Economic evaluation of a cluster randomized trial of interventions to improve health workers' practice in diagnosing and treating uncomplicated malaria in Cameroon.

Mangham-Jefferies L[1], Wiseman V[2], Achonduh OA[3], Drake TL[4], Cundill B[5], Onwujekwe O[6], Mbacham W[3].

Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK; Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK.; Laboratory for Public Health Research Biotechnologies, University of Yaoundé I, The Biotechnology Center, Yaoundé, Cameroon.;

Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK; Nuffield Department of Clinical Medicine, University of Oxford, Old Road Campus, Oxford, UK; Faculty of Tropical Medicine, Mahidol University, Rajwithi Road, Bangkok, Thailand.; Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK.; Department of Health Administration and Management, College of Medicine, University of Nigeria (Enugu Campus), Enugu, Nigeria.

BACKGROUND:

Malaria rapid diagnostic tests (RDTs) are a valid alternative to malaria testing with microscopy and are recommended for the testing of febrile patients before prescribing an antimalarial. There is a need for interventions to support the uptake of RDTs by health workers.

OBJECTIVE:

To evaluate the cost-effectiveness of introducing RDTs with basic or enhanced training in health facilities in which microscopy was available, compared with current practice.

METHODS:

A three-arm cluster randomized trial was conducted in 46 facilities in central and northwest Cameroon. Basic training had a practical session on RDTs and lectures on malaria treatment guidelines. Enhanced training included small-group activities designed to change health workers' practice and reduce the consumption of antimalarials among test-negative patients. The primary outcome was the proportion of febrile patients correctly treated: febrile patients should be tested for malaria, artemisinin combination therapy should be prescribed for confirmed cases, and no antimalarial should be prescribed for patients who are test-negative. Individual patient data were obtained from facility records and an exit survey. Costs were estimated from a societal perspective using project reports and patient exit data. The analysis used bivariate multilevel modeling and adjusted for imbalance in baseline covariates.

RESULTS:

Incremental cost per febrile patient correctly treated was $8.40 for the basic arm and $3.71 for the enhanced arm. On scale-up, it was estimated that RDTs with enhanced training would save $0.75 per additional febrile patient correctly treated.

CONCLUSIONS:

Introducing RDTs with enhanced training was more cost-effective than RDTs with basic training when each was compared with current practice.

Malar J. 2014 Jul 15;13:275. doi: 10.1186/1475-2875-13-275.

Thiamin supplementation does not reduce the frequency of adverse events after anti-malarial therapy among patients with falciparum malaria in southern Laos.

Mayxay M[1], Khanthavong M, Cox L, Sichanthongthip O, Imwong M, Pongvongsa T, Hongvanthong B, Phompida S, Vanisaveth V, White NJ, Newton PN.

Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao People's Democratic Republic.

BACKGROUND:

In a recent study one third of Lao patients presenting with uncomplicated Plasmodium falciparum malaria had biochemical evidence of thiamin deficiency, which was associated with a higher incidence of adverse events. Thiamin supplementation might, therefore, reduce adverse events in this population.

METHODS:

An exploratory, double-blind, parallel group, placebo-controlled, superiority trial of thiamin supplementation in patients of all ages with uncomplicated and severe falciparum malaria was conducted in Xepon District, Savannakhet Province, southern Laos. Patients were randomly assigned to either oral thiamin 10 mg/day for 7 days immediately after standard anti-malarial treatment then 5 mg daily until day 42, or identical oral placebo.

RESULTS:

After interim analyses when 630 patients (314 in thiamin and 316 in placebo groups) had been recruited, the trial was discontinued on the grounds of futility. On admission biochemical thiamin deficiency (alpha ≥ 25%) was present in 27% of patients and 9% had severe deficiency (alpha > 31%). After 42 days of treatment, the frequency of thiamin deficiency was lower in the thiamin (2%, 1% severe) compared to the placebo (11%, 3% severe) groups ($p < 0.001$ and $p = 0.05$), respectively. Except for diarrhoea, 7% in the placebo compared to 3% in the thiamin group ($p = 0.04$), and dizziness on day 1 (33% vs 25%, $p = 0.045$), all adverse events were not significantly different between the groups ($p > 0.05$). Clinical, haematological, and parasitological responses to treatment did not differ significantly between the two groups.

CONCLUSION:

Thiamin supplementation reduced biochemical thiamin deficiency among Lao malaria patients following anti-malarial drug treatment, but it did not reduce the frequency of adverse events after anti-malarial therapy or have any detected clinical or parasitological impact.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105794/pdf/1475-2875-13-275.pdf

Treatment of severe or complicated malaria

Cochrane Database Syst Rev. 2014 Sep 11;9:CD010678. doi: 10.1002/14651858.CD010678.pub2.

Artemether for severe malaria.

Esu E[1], Effa EE, Opie ON, Uwaoma A, Meremikwu MM.

Department of Public Health, University of Calabar, Calabar, Nigeria.

BACKGROUND:

In 2011 the World Health Organization (WHO) recommended parenteral artesunate in preference to quinine as first-line treatment for people with severe malaria. Prior to this recommendation, many countries, particularly in Africa, had begun to use artemether, an alternative artemisinin derivative. This review evaluates intramuscular artemether compared with both quinine and artesunate.

OBJECTIVES:

To assess the efficacy and safety of intramuscular artemether versus any other parenteral medication in treating severe malaria in adults and children.

SEARCH METHODS:

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE and LILACS, ISI Web of Science, conference proceedings and reference lists of articles. We also searched the WHO clinical trial registry platform, ClinicalTrials.gov and the metaRegister of Controlled Trials (mRCT) for ongoing trials up to 9 April 2014.

SELECTION CRITERIA:

Randomized controlled trials (RCTs) comparing intramuscular artemether with intravenous or intramuscular antimalarial for treating severe malaria.

DATA COLLECTION AND ANALYSIS:

The primary outcome was all-cause death.Two authors independently assessed trial eligibility, risk of bias and extracted data. We summarized dichotomous outcomes using risk ratios (RR) and continuous outcomes using mean differences (MD), and presented both measures with 95% confidence intervals (CI). Where appropriate, we combined data in meta-analyses and assessed the quality of the evidence using the GRADE approach.

MAIN RESULTS:

We included 18 RCTs, enrolling 2662 adults and children with severe malaria, carried out in Africa (11) and in Asia (7). Artemether versus quinine For children in Africa, there is probably little or no difference in the risk of death between intramuscular artemether and quinine (RR 0.96, 95% CI 0.76 to 1.20; 12 trials, 1447 participants, moderate quality evidence). Coma recovery may be about five hours shorter with artemether (MD -5.45, 95% CI -7.90 to -3.00; six trials, 358 participants, low quality evidence), and artemether may result in fewer neurological sequelae, but larger trials would be needed to confirm this (RR 0.84, 95% CI 0.66 to 1.07; seven trials, 968 participants, low quality evidence). Artemether probably shortens the parasite clearance time by about nine hours (MD -9.03, 95% CI -11.43 to -6.63; seven trials, 420 participants, moderate quality evidence), and may shorten the fever clearance time by about three hours (MD -3.73, 95% CI -6.55 to -0.92; eight trials, 457 participants, low quality evidence).For adults in Asia, treatment with intramuscular artemether probably results in fewer deaths than treatment with quinine (RR 0.59, 95% CI 0.42 to 0.83; four trials, 716 participants, moderate quality evidence). Artemether versus artesunate Artemether and artesunate have not been directly compared in randomized trials in African children.For adults in Asia, mortality is probably higher with intramuscular artemether (RR 1.80, 95% CI 1.09 to 2.97, two trials,494 participants, moderate quality evidence).

AUTHORS' CONCLUSIONS:

Although there is a lack of direct evidence comparing artemether with artesunate, artemether is probably less effective than artesunate at preventing deaths from severe malaria. In circumstances where artesunate is not available, artemether is an alternative to quinine.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455227/pdf/CD010678-0001.pdf

Treatment of vivax malaria

Am J Trop Med Hyg. 2014 Jul;91(1):18-26. doi: 10.4269/ajtmh.13-0053. Epub 2014 Apr 21.

Efficacy of three different regimens of primaquine for the prevention of relapses of Plasmodium vivax malaria in the Amazon Basin of Peru.

Durand S[1], Cabezas C[2], Lescano AG[2], Galvez M[2], Gutierrez S[2], Arrospide N[2], Alvarez C[2], Santolalla ML[2], Bacon DJ[2], Graf PC[2].

US Naval Medical Research Unit No. 6 (NAMRU-6), Lima and Iquitos, Peru; Instituto Nacional de Salud, Lima, Peru; Universidad Nacional Mayor de San Marcos, Lima, Peru; Universidad Peruana Cayetano Heredia, Lima, Peru; Direccion Regional de Salud Loreto, Iquitos, Peru; US Naval Medical Center San Diego, San Diego, California.

Abstract

We evaluated the efficacy of three primaquine (PQ) regimes to prevent relapses with Plasmodium vivax through an open-label randomized trial in Loreto, Peru. Vivax monoinfections were treated with chloroquine for 3 days and PQ in three different regimes: 0.5 mg/kg per day for 5 days (150 mg total), 0.5 mg/kg per day for 7 days (210 mg total), or 0.25 mg/kg per day for 14 days (210 mg total). Biweekly fever assessments and bimonthly thick smears were taken for 210 days. Recurrences after 35 days were considered relapses. One hundred eighty cases were enrolled in each group; 90% of cases completed follow-up. There were no group-related differences in age, sex, or parasitemia. Relapse rates were similar in the 7- and 14-day regimes (16/156 = 10.3% and 22/162 = 13.6%, P = 0.361) and higher in the 5-day group (48/169 = 28.4%, P < 0.001 and P = 0.001, respectively). The 7-day PQ regimen used in Peru is as efficacious as the recommended 14-day regimen and superior to 5 treatment days.

Malnutrition

(Papers 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)

Am J Clin Nutr. 2015 Mar;101(3):632-45. doi: 10.3945/ajcn.113.069807. Epub 2015 Jan 7.

Malian children with moderate acute malnutrition who are treated with lipid-based dietary supplements have greater weight gains and recovery rates than those treated with locally produced cereal-legume products: a community-based, cluster-randomized trial.

Ackatia-Armah RS[1], McDonald CM[1], Doumbia S[1], Erhardt JG[1], Hamer DH[1], Brown KH[1].

From the Program in Nutrition and Metabolism, Boston University School of Medicine, Boston, MA (RSA-A and DHH); Helen Keller International, New York, NY (RSA-A and KHB); the Program in International and Community Nutrition, University of California, Davis, CA (RSA-A and KHB); the Division of GI/Nutrition, Boston Children's Hospital, Boston, MA (CMM); the Department of Public Health, Faculty of Medicine, University of Bamako, Bamako, Mali (SD); the University of Indonesia, Jakarta, Indonesia (JGE); the Center for Global Health and Development, Boston University, Boston, MA (DHH); and the Department of Global Health, Boston University School of Public Health, Boston, MA (DHH).

BACKGROUND:

Moderate acute malnutrition (MAM), defined as weight-for-length z score between -3 and -2 or midupper arm circumference between 11.5 and 12.5 cm, affects ~33 million children aged <5 y worldwide.

OBJECTIVE:

The objective was to compare the effects of 4 dietary supplements for the treatment of MAM.

DESIGN:

Twelve community health centers in rural Mali were randomly assigned to provide to 1264 MAM children aged 6-35 mo one of 4 dietary supplements containing ~500 kcal/d for 12 wk: 1) ready-to-use, lipid-based supplementary food (RUSF); 2) special corn-soy blend (CSB++); 3) locally processed, fortified flour (Misola); or 4) locally milled flours plus oil, sugar, and micronutrient powder (LMF).

RESULTS:

In total, 1178 children (93.2%) completed the study. The adjusted mean (95% CI) change in weight (kg) from baseline was greater with RUSF than with the locally processed blends and was intermediate with CSB++ [1.16 (1.08, 1.24) for RUSF, 1.04 (0.96, 1.13) for CSB++, 0.91 (0.82, 0.99) for Misola, and 0.83 (0.74, 0.92) for LMF; $P < 0.001$]. For length change, RUSF and CSB++ differed significantly from LMF. Sustained recovery rates were higher with RUSF (73%) than with Misola (61%) and LMF (58%), $P < 0.0001$; CSB++ recovery rates (68%) did not differ from any of the other groups.

CONCLUSIONS:

RUSF was more effective, but more costly, than other dietary supplements for the treatment of MAM; CSB++ yielded intermediate results. The benefits of treatment should be considered in relation to product costs and availability.

Am J Clin Nutr. 2014 Jul;100(1):241-9. doi: 10.3945/ajcn.113.072538. Epub 2014 May 7.

Treating moderate acute malnutrition in first-line health services: an effectiveness cluster-randomized trial in Burkina Faso.

Nikièma L[1], Huybregts L[1], Kolsteren P[1], Lanou H[1], Tiendrebeogo S[1], Bouckaert K[1], Kouanda S[1], Sondo B[1], Roberfroid D[1].

From the Institut de Recherche en Sciences de la Santé, Ministry of Scientific Research and Innovation, Ouagadougou, Burkina Faso (LN, HL, ST, SK, and BS); the Child Health and Nutrition Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium (DR, LH, and PK); and the Department of Food Safety and Food Quality, Ghent University, Ghent, Belgium (LH, KB, and PK).

BACKGROUND:

Management of moderate acute malnutrition (MAM) is, currently, focused on food supplementation approaches. However, the sustainability of these strategies remains weak in low- and middle-income countries. In food-secure settings, an educational/behavioral intervention could be an alternative for improving MAM management.

OBJECTIVE:

This study compared the effectiveness of weekly context-appropriate child-centered counseling (CCC), with an improved corn-soy blend [corn-soy blend with added micronutrients (CSB++)]

or a locally produced ready-to-use supplementary food (RUSF), in treating MAM through first-line rural health services.

DESIGN:

We used a cluster randomized controlled trial design with 3 arms, involving 18 rural health centers (6 by arm) and children aged 6-24 mo with uncomplicated MAM. In the first arm (CCC), trained health workers provided weekly personalized counseling to caretakers. In the 2 other arms, children received weekly either 455 g CSB++ or 350 g locally produced soy-based RUSF. Both food supplements provided ~250 kcal/d.

RESULTS:

The recovery rate after 3 mo of treatment was significantly lower with CCC (57.8%) than with CSB++ (74.5%) and RUSF (74.2%) ($P < 0001$). Mothers' attendance at health facilities was also substantially lower in the CCC arm ($P < 0001$); this arm had a high defaulter rate ($P < 0.003$). When the analysis was adjusted for attendance, we did not find a significant difference between the 3 arms, with incidence rate ratios of 1.14 (95% CI: 0.99, 1.31) and 1.13 (95% CI: 0.98, 1.30) for the CSB++ and RUSF arms, respectively, compared with the CCC arm.

CONCLUSION:

Whereas supplement-based treatment of MAM was found to be more effective than the provision of CCC, we hypothesize that appropriate and specific nutrition counseling centered on children's needs, through primary health facilities, might be an alternative strategy for MAM treatment in rural food-secure areas, provided that attendance at counseling sessions by the caregiver is ensured.

http://ajcn.nutrition.org/content/100/1/241.full.pdf+html

Matern Child Nutr. 2014 Jul;10(3):436-51. doi: 10.1111/mcn.12112. Epub 2014 Feb 13.

Effectiveness of milk whey protein-based ready-to-use therapeutic food in treatment of severe acute malnutrition in Malawian under-5 children: a randomised, double-blind, controlled non-inferiority clinical trial.

Bahwere P[1], Banda T, Sadler K, Nyirenda G, Owino V, Shaba B, Dibari F, Collins S.

Valid International, Oxford, UK; Centre of Research in Epidemiology, Biostatistics and Clinical Research, School of Public Health, Free University of Brussels, Brussels, Belgium.

Abstract

The cost of ready-to-use therapeutic food (RUTF) used in community-based management of acute malnutrition has been a major obstacle to the scale up of this important child survival strategy. The current standard recipe for RUTF [peanut-based RUTF (P-RUTF)] is made from peanut paste, milk powder, oil, sugar, and minerals and vitamins. Milk powder forms about 30% of the ingredients and may represent over half the cost of the final product. The quality of whey protein concentrates 34% (WPC34) is similar to that of dried skimmed milk (DSM) used in the standard recipe and can be 25-33% cheaper. This blinded, parallel group, randomised, controlled non-inferiority clinical trial tested the effectiveness in treating severe acute malnutrition (SAM) of a new RUTF formulation WPC-RUTF in which WPC34 was used to replace DSM. Average weight gain (non-inferiority margin $\Delta = -1.2$ g kg(-1) day(-1)) and recovery rate ($\Delta = -10\%$)

were the primary outcomes, and length of stay (LOS) was the secondary outcome (Δ = +14 days). Both per-protocol (PP) and intention-to-treat (ITT) analyses showed that WPC-RUTF was not inferior to P-RUTF for recovery rate [difference and its 95% confidence interval (CI) of 0.5% (95% CI -2.7, 3.7) in PP analysis and 0.6% (95% CI -5.2, 6.3) in ITT analysis] for average weight gain [0.2 (-0.5; 0.9) for both analyses] and LOS [-1.6 days (95% CI, -4.6, 1.4 days) in PP analysis and -1.9 days (95% CI, -4.6, 0.8 days) for ITT analysis]. In conclusion, whey protein-based RUTF is an effective cheaper alternative to the standard milk-based RUTF for the treatment of SAM.

Maternal care

BMC Health Serv Res. 2014 Oct 18;14:483. doi: 10.1186/1472-6963-14-483.

Determinants of perceived quality of obstetric care in rural Tanzania: a cross-sectional study.

Larson E[1], Hermosilla S, Kimweri A, Mbaruku GM, Kruk ME.

Health Policy & Management, Columbia University, New York, USA.

BACKGROUND:

Patients' reported opinions of the health system need to be understood in order to provide patient-centered care. We investigated determinants of women's ratings of the quality of care during their most recent facility delivery.

METHODS:

We conducted a census of all deliveries in the 6 weeks to 12 months preceding the survey, in villages served by 24 primary care clinics in rural Pwani Region, Tanzania. Women who had delivered children in a study facility were included in this analysis (n = 855). We interviewed women about demographic and obstetric factors and the quality of their obstetric care using a structured questionnaire. We created a composite index of perceived quality from six quality questions. We also assessed the functioning of the local health clinic using structured surveys. We used a multi-level model to analyze factors associated with women's rating of the quality of care during delivery.

RESULTS:

14% of respondents rated the overall quality of care received during delivery as excellent. Women who listened to the radio daily reported lower quality composite scores (β: -0.99, $p < 0.001$). Women who reported receiving more services in ANC had higher quality scores (β: 0.46, $p = 0.001$), as did women receiving more delivery services (β: 0.55, $p < 0.001$). Women who reported disrespect and abuse during delivery had significantly lower quality scores (β: -4.13, $p < 0.001$).

CONCLUSIONS:

A woman's expectations and prior and current experiences influence her perception of the quality of care she received. Health facility characteristics did not influence ratings of overall

quality. Focusing on improving the process rather than inputs of service delivery during ANC visits and delivery may increase perceived quality of delivery care in low-resource settings.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283093/pdf/12913_2014_Article_3558.pdf

BMC Pregnancy Childbirth. 2014 Sep 5;14:308. doi: 10.1186/1471-2393-14-308.

Induction of labour in pre-eclamptic women: a randomised trial comparing the Foley balloon catheter with oral misoprostol.

Bracken H[1], Mundle S, Faragher B, Easterling T, Haycox A, Turner M, Alfirevic Z, Winikoff B, Weeks A.

Gynuity Health Projects, New York, USA.

BACKGROUND:

Between 40,000 and 80,000 pregnant women die annually from pre-eclampsia and eclampsia. Although magnesium sulphate and anti-hypertensive therapies can reduce the morbidity and mortality associated with pre-eclampsia, the only cure comes with delivery. Prompt delivery of the baby, preferably by vaginal route, is vital in order to achieve good maternal and neonatal outcomes. Induction of labour is therefore a critical intervention in order to prevent morbidity to both mother and baby. Two low cost interventions - oral misoprostol tablets and transcervical Foley catheterization - are already used by some in low resource settings, but their relative risks and benefits are not known. The trial will compare the risks, benefits, and trade-offs in efficacy, safety, acceptability and cost of misoprostol and Foley catheter for induction in women with preeclampsia or uncontrolled hypertension.

METHODS/DESIGN:

A total of 602 women with an ongoing pregnancy with a live fetus requiring delivery because of pre-eclampsia or uncontrolled hypertension will be randomly assigned to labor induction with a transcervical Foley catheter or oral misoprostol 25 micrograms. Women will be recruited at two hospitals in Nagpur, India. The misoprostol group will receive oral misoprostol 25 microgram every 2 hours for a maximum of 12 doses or until active labor commences. The Foley group will undergo induction using a Foley catheter (silicone, size 18 F with 30 ml balloon) which will remain until active labor starts, the Foley catheter falls out, or 12 hours have elapsed. The primary outcome will be the attainment of vaginal delivery within 24 hours. Providers administering the treatment and those assessing the outcomes will not be blinded to group assignment.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4261642/pdf/12884_2014_Article_1245.pdf

Am J Clin Nutr. 2015 Mar;101(3):523-9. doi: 10.3945/ajcn.114.092585. Epub 2014 Dec 24.

Association of cesarean delivery with anemia in infants and children in 2 large longitudinal Chinese birth cohorts.

Li HT[1], Trasande L[1], Zhu LP[1], Ye RW[1], Zhou YB[1], Liu JM[1].

From the Institute of Reproductive and Child Health/Ministry of Health Key Laboratory of Reproductive Health (H-tL, R-wY, Y-bZ, and J-mL) and the Department of Epidemiology and Biostatistics (H-tL and J-mL), School of Public Health, Peking University Health Science Center, Beijing, China; the Departments of Pediatrics, Environmental Medicine, and Population Health, School of Medicine, Wagner School of Public Service, and Steinhardt School of Culture, Education, and Human Development, New York University, New York, NY (LT); and the Shanghai First Maternity and Infant Hospital (affiliated with Tongji University), Shanghai Women's Health Institute, Shanghai, China

BACKGROUND:

Cesarean delivery may reduce placental-fetal transfusion and thus increase the risk of early childhood anemia compared with vaginal delivery, but this notion has not been carefully studied in longitudinal cohorts.

OBJECTIVE:

The aim was to assess the association of cesarean delivery with anemia in infants and children in 2 longitudinal Chinese birth cohorts from different socioeconomic settings.

DESIGN:

Cohort 1 was recruited from 5 counties in northeastern China and cohort 2 from 21 counties or cities in southeastern China. Cohort 1 involved 17,423 infants born during 2006-2009 to mothers with early pregnancy baseline hemoglobin concentrations ranging from 100 to 177 g/L, whereas cohort 2 involved 122,777 children born during 1993-1996 to mothers with baseline hemoglobin concentrations ranging from 60 to 190 g/L. The main outcomes were anemia at 6 and 12 mo in cohort 1 and at 58 mo in cohort 2. Multiple logistic regressions were used to estimate adjusted ORs of anemia for cesarean compared with vaginal delivery. Stratified analyses were performed by pre- and postlabor cesarean delivery and according to maternal baseline hemoglobin concentration (≤109, 110-119, 120-129, and ≥130 g/L).

RESULTS:

Cesarean delivery was not associated with anemia at 6 mo in cohort 1 (adjusted OR: 1.05; 95% CI: 0.93, 1.19); however, cesarean delivery was associated with increased anemia at 12 mo in cohort 1 (adjusted OR: 1.19; 95% CI: 1.04, 1.37) and at 58 mo in cohort 2 (adjusted OR: 1.11; 95% CI: 1.08, 1.15). The positive associations for anemia at 12 and 58 mo were consistent across maternal hemoglobin subgroups and persisted for cesarean delivery subtypes.

CONCLUSION:

Cesarean delivery is likely associated with anemia in children, which suggests a possible need for exploring changes in obstetric care that might prevent anemia in cesarean-delivered children.

PLoS Med. 2014 Sep 23;11(9):e1001735. doi: 10.1371/journal.pmed.1001735. eCollection 2014.

Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial.

González R[1], Desai M[2], Macete E[3], Ouma P[4], Kakolwa MA[5], Abdulla S[5], Aponte JJ[1], Bulo H[3], Kabanywanyi AM[5], Katana A[4], Maculuve S[3], Mayor A[1], Nhacolo A[3], Otieno K[4], Pahlavan G[6], Rupérez M[1], Sevene E[3], Slutsker L[7], Vala A[3], Williamsom J[2], Menéndez C[1].

Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-Universitat de Barcelona), ISGlobal, Barcelona Institute for Global Health, Barcelona, Spain; Manhiça Health Research Center Manhiça, Mozambique.; Kenya Medical Research Institute/Centers for Disease Control and Prevention (KEMRI/CDC) Research and Public Health Collaboration, Kisumu, Kenya; Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, and Kisumu, Kenya.; Manhiça Health Research Center (CISM), Manhiça, Mozambique.; Kenya Medical Research Institute/Centers for Disease Control and Prevention (KEMRI/CDC) Research and Public Health Collaboration, Kisumu, Kenya; Kenya Medical Research Institute (KEMRI)/Center for Global Health Research, Kisumu, Kenya.; Ifakara Health Institute (IHI), Dodoma, Tanzania.; Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, and Kisumu, Kenya.

BACKGROUND:

Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is recommended for malaria prevention in HIV-negative pregnant women, but it is contraindicated in HIV-infected women taking daily cotrimoxazole prophylaxis (CTXp) because of potential added risk of adverse effects associated with taking two antifolate drugs simultaneously. We studied the safety and efficacy of mefloquine (MQ) in women receiving CTXp and long-lasting insecticide treated nets (LLITNs).

METHODS AND FINDINGS:

A total of 1,071 HIV-infected women from Kenya, Mozambique, and Tanzania were randomized to receive either three doses of IPTp-MQ (15 mg/kg) or placebo given at least one month apart; all received CTXp and a LLITN. IPTp-MQ was associated with reduced rates of maternal parasitemia (risk ratio [RR], 0.47 [95% CI 0.27-0.82]; p=0.008), placental malaria (RR, 0.52 [95% CI 0.29-0.90]; p=0.021), and reduced incidence of non-obstetric hospital admissions (RR, 0.59 [95% CI 0.37-0.95]; p=0.031) in the intention to treat (ITT) analysis. There were no differences in the prevalence of adverse pregnancy outcomes between groups. Drug tolerability was poorer in the MQ group compared to the control group (29.6% referred dizziness and 23.9% vomiting after the first IPTp-MQ administration). HIV viral load at delivery was higher in the MQ group compared to the control group (p=0.048) in the ATP analysis. The frequency of perinatal mother to child transmission of HIV was increased in women who received MQ (RR, 1.95 [95% CI 1.14-3.33]; p=0.015). The main limitation of the latter finding relates to the exploratory nature of this part of the analysis.

CONCLUSIONS:

An effective antimalarial added to CTXp and LLITNs in HIV-infected pregnant women can improve malaria prevention, as well as maternal health through reduction in hospital admissions. However, MQ was not well tolerated, limiting its potential for IPTp and indicating the need to find alternatives with better tolerability to reduce malaria in this particularly vulnerable group. MQ was associated with an increased risk of mother to child transmission of HIV, which

warrants a better understanding of the pharmacological interactions between antimalarials and antiretroviral drugs.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4172537/pdf/pmed.1001735.pdf

J Int Assoc Provid AIDS Care. 2014 Jul-Aug;13(4):335-41.

Group problem-solving therapy for postnatal depression among HIV-positive and HIV-negative mothers in Zimbabwe.

Chibanda D, Shetty AK, Tshimanga M, Woelk G, Stranix-Chibanda L, Rusakaniko S.

Postnatal depression (PND) is a major problem in low- and middle-income countries (LMICs). A total of 210 postpartum mothers attending primary care urban clinics were screened for PND at 6 weeks postpartum using the Edinburgh Postnatal Depression Scale (EPDS) and Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition; DSM-IV) criteria for major depression. The HIV prevalence was 14.8%. Of the 210 enrolled postpartum mothers, 64 (33%) met DSM IV criteria for depression. Using trained peer coun- selors, mothers with PND (n = 58) were randomly assigned to either group problem-solving therapy (PST, n = 30) or amitriptyline (n = 28). Of the 58 mothers with PND, 49 (85%) completed 6 weeks of group PST (n = 27) or pharmacotherapy (n = 22). At baseline, the mean EPDS score for participants randomized to group PST was 17.3 (standard deviation [SD] 3.7), while the group randomized to amitriptyline had a mean EPDS score of 17.9 (SD 3.9; P = .581). At 6 weeks postintervention, the drop in mean EPDS score was greater in the PST group (8.22, SD 3.6) compared to the amitriptyline group (10.7, SD 2.7; P = .0097). Group PST using peer counselors is feasible, acceptable, and more effective compared to pharmacotherapy in the treatment of PND. Group PST could be integrated into maternal and child health clinics and preventing mother-to-child transmission of HIV programs in LMICs.

Contraception. 2015 May 19. pii: S0010-7824(15)00220-6. doi: 10.1016/j.contraception.2015.05.008. [Epub ahead of print]

A Randomised Non-inferiority Crossover Controlled Trial of the Functional Performance and Safety of New Female Condoms: An Evaluation of the Velvet, Cupid2 and FC2.

Beksinska M[1], Greener R[2], Kleinschmidt I[3], Pillay L[2], Maphumulo V[2], Smit J[4].

MatCH Research [Maternal, Adolescent and Child Health Research], Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, South Africa; Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, ; MatCH Research Maternal, Adolescent and Child Health Research], Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, 34 Essex Terrace, Westville, Durban, 3629, South Africa.; Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E, UK.; MatCH Research [Maternal, Adolescent and Child Health Research], Department of Obstetrics and Gynaecology, Faculty of Health Sciences, University of the Witwatersrand, 34 Essex

Terrace, Westville, Durban, 3629, South Africa; School of Pharmacy and Pharmacology, Faculty of Health Sciences, University of KwaZulu-Natal, University Road,South Africa.

OBJECTIVES:

New designs of female condoms have been developed to lower cost and/or improve acceptability. To secure regulatory approvals, clinical studies are required to verify performance. We aimed to assess the functional performance and safety of two new female condom types- Velvet, and Cupid2 female condom-against the existing FC2 female condom.

STUDY DESIGN:

This was a three-period crossover, randomized non-inferiority clinical trial with 300 women randomized to condom type order in one South African site. Primary endpoints were total clinical failure and total female condom failure. Non-inferiority of component modes, clinical breakage, non-clinical breakage, slippage, misdirection, and invagination were also determined. Safety data were also assessed for each female condom. Participants were asked to use 5 of each female condom type, collect information on use in a condom diary at home and were interviewed after use of each type. Frequencies and percentages were calculated by condom type for each failure mode and differences in performance of the 3 female condoms using FC2 as reference, with 95% CIs, were estimated using GEE models.

RESULTS:

282 (94%) completed follow-up, using at least one condom of each type. Total clinical failure (clinical breakage, invagination, misdirection, slippage) was <5% for all female condoms:- FC2 (4.50%); Cupid2 (4.79%) and Velvet (3.93%). Non-inferiority was demonstrated for all condom failure modes for the two new female condoms with respect to FC2 within the margin of 3% difference in mean failure, at the 5% significance level.

CONCLUSION:

Non-inferiority for the two new female condoms was demonstrated with respect to the marketed FC2. These data are used to support manufacturer dossiers for WHO/UNFPA pre-qualification.

IMPLICATIONS:

Data from this study has been submitted to WHO/UNFPA and will contribute to the prequalification submission requirements for the Cupid2 and Velvet female condoms.

Maternal nutrition and micronutrient supplementation

J Nutr. 2015 Mar;145(3):634-9. doi: 10.3945/jn.114.203448. Epub 2015 Jan 14.

Seasonality modifies the effect of a lipid-based nutrient supplement for pregnant rural women on birth length.

Toe LC[1], Bouckaert KP[2], De Beuf K[3], Roberfroid D[4], Meda N[5], Thas O[6], Van Camp J[7], Kolsteren PW[2], Huybregts LF[8].

Departments of Food Safety and Food Quality and Centre Muraz, Ministry of Health, Bobo-Dioulasso, Burkina Faso; Departments of Food Safety and Food Quality and Nutrition and Child Health Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium;

Mathematical Modeling, Statistics, and Bioinformatics, and FIRE Statistical Consulting, Ghent University, Ghent, Belgium; Nutrition and Child Health Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium; Centre Muraz, Ministry of Health, Bobo-Dioulasso, Burkina Faso; Mathematical Modeling, Statistics, and Bioinformatics, and National Institute for Applied Statistics Research, School of Mathematics and Applied Statistics, University of Wollongong, Wollongong, Australia; Departments of Food Safety and Food Quality and.; Departments of Food Safety and Food Quality and Nutrition and Child Health Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium; Poverty, Health, and Nutrition Division, International Food Policy Research Institute, Washington, DC

BACKGROUND:

Maternal nutritional status is a major determinant of low birth weight and fluctuates across seasons. Seasonality may influence the outcome of prenatal nutrition interventions that aim to enhance fetal growth.

OBJECTIVE:

This study investigated seasonal modifications of the efficacy of a randomized controlled prenatal nutrition intervention trial in pregnant women to improve fetal growth in rural Burkina Faso.

METHODS:

The second Micronutriments et Santé de la Mère et de l'Enfant study compared a lipid-based nutrient supplement (LNS) fortified with multiple micronutrients (MMNs) to an MMN supplement. Truncated Fourier series were used to characterize seasonality in birth outcomes. Models that included the Fourier series and newborn and maternal characteristics were used to assess seasonal effect modifications of prenatal supplementation on birth outcomes.

RESULTS:

Birth weight, birth length, small for gestational age as a proxy for intrauterine growth retardation, and preterm birth were significantly related to date of birth and showed important seasonal variations. LNSs, which supply energy in addition to MMNs, resulted in a significant increase in birth length (+13.5 mm, 95% CI: 6.5, 20.5 mm) at the transition from rain to dry season (September to November) compared to MMNs alone.

CONCLUSIONS:

The climatologic and agricultural seasonal patterns in Burkina Faso affect the efficacy of prenatal LNSs on birth length. In this context, prenatal MMN supplementation programs should be complemented by energy supplementation during the annual rain season to promote fetal growth. This trial was registered at clinicaltrials.gov as NCT00909974.

Am J Clin Nutr. 2015 Feb;101(2):387-97. doi: 10.3945/ajcn.114.088617. Epub 2014 Dec 10.

The impact of lipid-based nutrient supplement provision to pregnant women on newborn size in rural Malawi: a randomized controlled trial.

Ashorn P[1], Alho L[1], Ashorn U[1], Cheung YB[1], Dewey KG[1], Harjunmaa U[1], Lartey A[1], Nkhoma M[1], Phiri N[1], Phuka J[1], Vosti SA[1], Zeilani M[1], Maleta K[1].

From the Department for International Health, University of Tampere School of Medicine, Tampere, Finland (PA, LA, UA, YBC, and UH); the Department of Paediatrics, Tampere University Hospital, Tampere, Finland (PA); Duke-National University of Singapore Graduate Medical School, Centre for Quantitative Medicine, Singapore, Singapore (YBC); the Departments of Nutrition (KGD) and Agricultural and Resource Economics (SAV), University of California, Davis, Davis, CA; the Department of Nutrition & Food Science, University of Ghana, Legon, Ghana (AL); the Department of Community Health, University of Malawi College of Medicine, Blantyre, Malawi (MN, NP, JP, and KM); and Nutriset S.A.S., Malaunay, France (MZ).

BACKGROUND:

Small birth size, often associated with insufficient maternal nutrition, contributes to a large share of global child undernutrition, morbidity, and mortality. We developed a small-quantity lipid-based nutrient supplement (SQ-LNS) to enrich the diets of pregnant women.

OBJECTIVE:

The objective was to test a hypothesis that home fortification of pregnant women's diets with SQ-LNS would increase birth size in an African community.

DESIGN:

We enrolled 1391 women with uncomplicated pregnancies (<20 gestational weeks) in a randomized controlled trial in Malawi. The women were provided with one daily iron-folic acid (IFA) capsule, one capsule containing multiple micronutrients (MMNs), or one 20-g sachet of SQ-LNS (LNS, containing 118 kcal, protein, carbohydrates, essential fatty acids, and 21 micronutrients). Primary outcomes were birth weight and newborn length. Secondary outcomes included newborn weight, head and arm circumference, and pregnancy duration. Analysis was by intention to treat.

RESULTS:

The mean ± SD birth weight and newborn length were 2948 ± 432, 2964 ± 460, and 3000 ± 447 g (P = 0.258) and 49.5 ± 2.4, 49.7 ± 2.2, and 49.9 ± 2.1 cm (P = 0.104) in the IFA, MMN, and LNS groups, respectively. For newborn weight-for-age, head circumference, and arm circumference, the point estimate for the mean was also highest in the LNS group, intermediate in the MMN group, and lowest in the IFA group, but except for midupper arm circumference (P = 0.024), the differences were not statistically significant. The prevalence of low birth weight (<2500 g) was 12.7%, 13.5%, and 12.1% (P = 0.856), respectively; newborn stunting (length-for-age z score < -2) was 19.2%, 14.0%, and 14.9% (P = 0.130), respectively; and newborn small head circumference (head circumference-for-age z score < -2) was 5.8%, 3.0%, and 3.1% (P = 0.099), respectively. The associations between the intervention and the outcomes were not modified by maternal parity, age, or nutritional status (P > 0.100).

CONCLUSION:

The study findings do not support a hypothesis that provision of SQ-LNS to all pregnant women would increase the mean birth size in rural Malawi.

J Nutr. 2015 Jun;145(6):1345-53. doi: 10.3945/jn.114.207225. Epub 2015 Apr 29.

Supplementation of Maternal Diets during Pregnancy and for 6 Months Postpartum and Infant Diets Thereafter with Small-Quantity Lipid-Based Nutrient Supplements Does Not Promote Child Growth by 18 Months of Age in Rural Malawi: A Randomized Controlled Trial.

Ashorn P[1], Alho L[2], Ashorn U[2], Cheung YB[3], Dewey KG[4], Gondwe A[5], Harjunmaa U[2], Lartey A[6], Phiri N[5], Phiri TE[6], Vosti SA[7], Zeilani M[8], Maleta K[5].

Department for International Health, University of Tampere School of Medicine, Tampere, Finland; Department of Paediatrics, Tampere University Hospital, Tampere, Finland; Department for International Health, University of Tampere School of Medicine, Tampere, Finland; Department for International Health, University of Tampere School of Medicine, Tampere, Finland; Centre for Quantitative Medicine, Duke-National University of Singapore Graduate Medical School, Singapore; Departments of Nutrition; Department of Community Health, University of Malawi College of Medicine, Blantyre, Malawi; Department of Nutrition & Food Science, University of Ghana, Accra, Ghana; and.; Agricultural and Resource Economics, University of California, Davis, Davis, CA; Department for External Research and Nutrition Strategies Nutriset S.A.S., Malaunay, France.

BACKGROUND:

Intrauterine growth restriction may be reduced by supplementing maternal diets during pregnancy, but few studies have assessed the impact of combined prenatal and postnatal interventions on child growth.

OBJECTIVE:

We tested a hypothesis that provision of small-quantity lipid-based nutrient supplements (SQ-LNSs) to mothers in pregnancy and 6 mo postpartum and to their infants from 6 to 18 mo of age would promote infant and child growth in the study area in rural Malawi.

METHODS:

We enrolled 869 pregnant women in a randomized trial in Malawi. During pregnancy and 6 mo thereafter, the women received daily 1 capsule of iron-folic acid (IFA), 1 capsule containing 18 micronutrients (MMN), or one 20-g sachet of SQ-LNS [lipid-based nutrient supplements (LNS), containing 21 MMN, protein, carbohydrates, essential fatty acids, and 118 kcal]. Children in the IFA and MMN groups received no supplementation; children in the LNS group received SQ-LNSs from 6 to 18 mo. Primary outcome was child length at 18 mo.

RESULTS:

At 18 mo, the mean length in the IFA, MMN, and LNS groups was 77.0, 76.9, and 76.8 cm ($P = 0.90$), respectively, and the prevalence of stunting was 32.7%, 35.6%, and 37.9% ($P = 0.54$), respectively. No intergroup differences were found in the mean weight, head circumference, or midupper arm circumference or the proportions with low z scores for these variables ($P > 0.05$). Covariate adjustment did not change the analysis results, and the associations between the intervention and child length were not modified by maternal parity, age, or nutritional status ($P > 0.10$).

CONCLUSIONS:

The findings do not support a hypothesis that provision of SQ-LNSs to women in pregnancy and postpartum and to children from 6 to 18 mo of age would promote child growth in this Malawian study area. This trial was registered at clinicaltrials.gov as NCT01239693.

Am J Clin Nutr. 2015 Apr;101(4):835-46. doi: 10.3945/ajcn.114.091546. Epub 2015 Feb 11.

Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana.

Adu-Afarwuah S[1], Lartey A[1], Okronipa H[1], Ashorn P[1], Zeilani M[1], Peerson JM[1], Arimond M[1], Vosti S[1], Dewey KG[1].

From the Department of Nutrition and Food Science, University of Ghana, Legon, Ghana (SA-A, AL, and HO); the Department for International Health, University of Tampere School of Medicine, Tampere, Finland (PA); Nutriset S.A.S., Malaunay, France (MZ); Department of Agricultural and Resource Economics, University of California, Davis, Davis, CA (SV); and the Program in International and Community Nutrition, Department of Nutrition, University of California, Davis, Davis, CA (JMP, MA, and KGD).

BACKGROUND:

The International Lipid-Based Nutrient Supplements Project developed a small-quantity (20 g/d) lipid-based nutrient supplement (LNS) for pregnant and lactating women.

OBJECTIVE:

We evaluated the effects of prenatal LNS supplementation on fetal growth.

DESIGN:

In a community-based, partially double-blind, individually randomized controlled trial, 1320 women ≤20 wk pregnant received 60 mg Fe/400 μg folic acid (IFA), or 1-2 Recommended Dietary Allowances of 18 micronutrients, including 20 mg Fe (MMN), or LNS with the same micronutrients as the MMN group, plus 4 minerals and macronutrients contributing 118 kcal (LNS) daily until delivery. Fetal growth was compared across groups by using intention-to-treat analysis. The primary outcome was birth length.

RESULTS:

This analysis included 1057 women (IFA = 349, MMN = 354, LNS = 354). Groups did not differ significantly in mean birth length, length-for-age z score (LAZ), head circumference, or percentage low birth length but differed in mean birth weight (P = 0.044), weight-for-age z score (WAZ; P = 0.046), and BMI-for-age z score (BMIZ; P = 0.040), with a trend toward differences in low birth weight (P = 0.069). In pairwise comparisons, the LNS group had greater mean birth weight (+85 g; P = 0.040), WAZ (+0.19; P = 0.045), and BMIZ (+0.21; P = 0.035) and a lower risk of low birth weight (RR: 0.61, 95% CI: 0.39, 0.96; P = 0.032) than did the IFA group. The other group differences were not significant. The effect of intervention was modified by mother's parity, age, height, baseline hemoglobin, household food insecurity, and child sex, with parity being the most consistent modifier. Among primiparous women (IFA = 131; MMN = 110; LNS = 128), the LNS group had greater mean birth length (+0.91 cm; P = 0.001), LAZ (+0.47; P = 0.001), weight (+237 g; P < 0.001), WAZ (+0.56; P < 0.001), BMIZ (+0.52; P < 0.001), head circumference (0.50 cm; P = 0.017), and head circumference-for-age z score (+0.40; P = 0.022) than did the IFA group; similar differences were found when comparing the LNS and MMN groups among primiparous women, and no group differences were found among multiparous women.

CONCLUSION:

Prenatal LNS supplementation can improve fetal growth among vulnerable women in Ghana, particularly primiparous women.

Am J Clin Nutr. 2014 Dec;100(6):1587-95. doi: 10.3945/ajcn.114.090621. Epub 2014 Oct 1.

Bioavailability of enteric-coated microencapsulated calcium during pregnancy: a randomized crossover trial in Bangladesh.

Roth DE[1], Pezzack B[1], Al Mahmud A[1], Abrams SA[1], Islam M[1], Aimone Phillips A[1], Baxter JA[1], Dimitris MC[1], Hawthorne KM[1], Ahmed T[1], Zlotkin SH[1].

From the Department of Pediatrics and Centre for Global Child Health, Hospital for Sick Children, Toronto, Ontario, Canada (DER, BP, AAP, J-ABB, MCD, and SHZ); the Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (DER and SHZ); the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh (AAM, MI, and TA); and the USDA/Agricultural Research Service Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX (SAA and KMH).

BACKGROUND:

Prenatal calcium and iron supplements are recommended in settings of low dietary calcium intake and high prevalence of anemia. However, calcium administration may inhibit iron absorption. To overcome calcium-iron interactions, we developed a multi-micronutrient powder containing iron (60 mg), folic acid (400 μg), and calcium carbonate granules microencapsulated with a pH-sensitive enteric coating to delay intestinal release.

OBJECTIVES:

We aimed to establish in vivo evidence that enteric-coated (EC) calcium is bioavailable in pregnant women and to explore the dose-responsiveness of fractional calcium absorption (FCA) in pregnancy.

DESIGN:

This was a randomized crossover trial in pregnant women (26-28 wk of gestation) in Dhaka, Bangladesh. Participants were allocated to 1 of 3 dose groups (500, 1000, or 1500 mg elemental Ca). FCA was estimated in random order for EC and non-EC (control) granules by a dual-stable-isotope method ((44)Ca-labeled granules and intravenous (42)Ca) on the basis of the relative recovery of (44)Ca compared with (42)Ca in urine over 48 h.

RESULTS:

Forty-nine participants with FCA for both EC and non-EC granules were included in the primary analyses. FCA geometric means were as follows: 21.8% (500 mg), 9.2% (1000 mg), and 11.7% (1500 mg) for non-EC granules compared with 3.3% (500 mg), 1.2% (1000 mg), and 2.1% for EC granules. Cumulative 48-h FCA of EC calcium was 85% lower ($P < 0.001$) than that of non-EC calcium, after adjustment for dose. In comparison to 500 mg, the FCA for the 1000-mg dose was 61% lower ($P < 0.001$) and was 42% lower ($P = 0.002$) for the 1500-mg dose, after adjustment for formulation.

CONCLUSIONS:

A pH-sensitive enteric coating substantially reduced calcium absorption from a prenatal multi-micronutrient powder. In its current formulation, this novel supplement is not suitable for clinical use. FCA was highly dose-dependent, such that doses of 1000 and 1500 mg delivered only negligibly more bioavailable calcium than the 500-mg dose.

Br J Nutr. 2014 Sep 28;112(6):908-15. doi: 10.1017/S0007114514001512. Epub 2014 Aug 4.

Prenatal vitamin D_3 supplementation suppresses LL-37 peptide expression in ex vivo activated neonatal macrophages but not their killing capacity.

Raqib R[1], Ly A[2], Akhtar E[1], Mily A[1], Perumal N[2], Al-Mahmud A[1], Rekha RS[1], Hel Baqui A[3], Roth DE[2].

Nutritional Biochemistry Laboratory, Centre for Vaccine Sciences, International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B), Dhaka,Bangladesh.; Department of Paediatrics,Hospital for Sick Children and University of Toronto,Toronto,ON,Canada ; Department of International Health,International Center for Maternal and Newborn Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore,M,USA.

Abstract

Vitamin D has regulatory effects on innate immunity. In the present study, we aimed to assess the effect of prenatal vitamin D_3 ($vitD_3$) supplementation on neonatal innate immunity in a randomised, placebo-controlled trial by evaluating cathelicidin (LL-37) expression and the killing capacity of macrophages. Healthy pregnant women (n 129) attending a clinic in Dhaka were randomised to receive either a weekly oral dose of 0·875 mg $vitD_3$ or placebo starting from 26 weeks of gestation up to delivery. Serum, plasma and monocyte-derived macrophages (MDM) were obtained from the cord blood. 25-Hydroxyvitamin D (25(OH)D) concentration was measured in serum. MDM were stimulated with or without Toll-like-receptor 4 ligand (TLR4L). Innate immune function was assessed by measuring LL-37 peptide levels in the culture supernatant of MDM by ELISA, LL-37 transcript levels by quantitative PCR, and ex vivo bactericidal capacity of MDM. $VitD_3$ supplementation did not increase LL-37 peptide levels in plasma or in the extracellular fluid of macrophages with or without TLR4L induction. However, stimulated intracellular LL-37 expression (ratio of stimulated:unstimulated MDM) was significantly reduced in the vitamin D group v. placebo (P=0·02). Multivariate-adjusted analyses showed that intracellular LL-37 peptide concentration from stimulated MDM was inversely associated with 25(OH)D concentration in serum (P=0·03). TLR4L stimulation increased the bactericidal capacity of MDM compared with the unstimulated ones (P=0·01); however, there was no difference in killing capacity between the two groups. A weekly dose of 0·875 mg $vitD_3$ to healthy pregnant women suppressed the intracellular LL-37 peptide stores of activated macrophages, but did not significantly affect the ex vivo bactericidal capacity of cord blood MDM.

Meningitis and encephalitis

PLoS One. 2015 Apr 17;10(4):e0122608. doi: 10.1371/journal.pone.0122608. eCollection 2015.

A preliminary randomized double blind placebo-controlled trial of intravenous immunoglobulin for Japanese encephalitis in Nepal.

Rayamajhi A[1], Nightingale S[2], Bhatta NK[3], Singh R[3], Ledger E[2], Bista KP[4], Lewthwaite P[2], Mahaseth C[5], Turtle L[2], Robinson JS[6], Galbraith SE[7], Wnek M[2], Johnson BW[6], Faragher B[8], Griffiths MJ[9], Solomon T[10].

Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom; National Academy of Medical Sciences, Kathmandu, Nepal; Kanti Children's Hospital, Kathmandu, Nepal; Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom; BP Koirala Institute of Health Sciences, Dharan, Nepal.; Kanti Children's Hospital, Kathmandu, Nepal.; National Academy of Medical Sciences, Kathmandu, Nepal; Kanti Children's Hospital, Kathmandu, Nepal.; Centers for Disease Control and Prevention, Division of Vector-Borne Diseases, Arbovirus Diseases Branch Diagnostic & Reference Laboratory, Fort Collins, Colorado, United States of America.; Institute for Health and Wellbeing, Leeds Metropolitan University, Leeds, United Kingdom.; Liverpool School of Tropical Medicine, Liverpool, United Kingdom.; Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom; Alder Hey Children's National Health Service Foundation Trust, Liverpool, United Kingdom.; Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom; The Walton Centre National Health Service Foundation Trust, Liverpool, United Kingdom; National Consortium for Zoonosis Research, Liverpool, United Kingdom; National Institute for Health Research-Health Protection Research Unit in Emerging and Zoonotic Infections, Liverpool, United Kingdom.

BACKGROUND:

Japanese encephalitis (JE) virus (JEV) is a mosquito-borne flavivirus found across Asia that is closely related to West Nile virus. There is no known antiviral treatment for any flavivirus. Results from in vitro studies and animal models suggest intravenous immunoglobulin (IVIG) containing virus-specific neutralizing antibody may be effective in improving outcome in viral encephalitis. IVIG's anti-inflammatory properties may also be beneficial.

METHODOLOGY/PRINCIPAL FINDINGS:

We performed a pilot feasibility randomized double-blind placebo-controlled trial of IVIG containing anti-JEV neutralizing antibody (ImmunoRel, 400mg/kg/day for 5 days) in children with suspected JE at two sites in Nepal; we also examined the effect on serum neutralizing antibody titre and cytokine profiles. 22 children were recruited, 13 of whom had confirmed JE; 11 received IVIG and 11 placebo, with no protocol violations. One child (IVIG group) died during treatment and two (placebo) subsequently following hospital discharge. Overall, there was no difference in outcome between treatment groups at discharge or follow up. Passive transfer of anti-JEV antibody was seen in JEV negative children. JEV positive children treated with IVIG had JEV-specific neutralizing antibody titres approximately 16 times higher than those treated with placebo (p=0.2), which was more than could be explained by passive transfer alone. IL-4 and IL-6 were higher in the IVIG group.

CONCLUSIONS/SIGNIFICANCE:

A trial of IVIG for JE in Nepal is feasible. IVIG may augment the development of neutralizing antibodies in JEV positive patients. IVIG appears an appealing option for JE treatment that warrants further study.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4401695/pdf/pone.0122608.pdf

Newborn care

Lancet. 2014 Jul 19;384(9939):235-40. doi: 10.1016/S0140-6736(14)60197-5. Epub 2014 Apr 17.

Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial.

Vain NE[1], Satragno DS[2], Gorenstein AN[3], Gordillo JE[4], Berazategui JP[2], Alda MG[5], Prudent LM[2].

School of Medicine, University of Buenos Aires, Buenos Aires, Argentina; Foundation for Maternal and Child Health (FUNDASAMIN), Buenos Aires, Argentina; Trinidad Palermo Private Hospital, Buenos Aires, Argentina.;

Foundation for Maternal and Child Health (FUNDASAMIN), Buenos Aires, Argentina; Trinidad Palermo Private Hospital, Buenos Aires, Argentina.; Institute of Maternity Our Lady of Mercy, San Miguel de Tucumán, Argentina.

BACKGROUND:

Delayed cord clamping allows for the passage of blood from the placenta to the baby and reduces the risk of iron deficiency in infancy. To hold the infant for more than 1 min at the level of the vagina (as is presently recommended), on the assumption that gravity affects the volume of placental transfusion, is cumbersome, might result in low compliance, and interferes with immediate contact of the infant with the mother. We aimed to assess whether gravity affects the volume of placental transfusion

METHODS:

We did a multicentre non-inferiority trial at three university-affiliated hospitals in Argentina. We obtained informed consent from healthy mothers with normal term pregnancies admitted early in labour. Vigorous babies born vaginally were randomly assigned in a 1:1 ratio by computer-generated blocks and sequentially numbered sealed opaque envelopes to be held for 2 min before clamping the umbilical cord, at the level of the vagina (introitus group) or on the mother's abdomen or chest (abdomen group). Newborn babies were weighed immediately after birth and after cord clamping. The primary outcome was the difference in weight (as a proxy of placental transfusion volume). The prespecified non-inferiority margin was 18 g (20%). We used t test and $\chi(2)$ test for group comparison, and used a multivariable linear regression analysis to control for covariables.

FINDINGS:

Between Aug 1, 2011, and Aug 31, 2012, we allocated 274 newborn babies to the introitus group and 272 to the abdomen group. 77 newborn babies in the introitus group and 78 in the abdomen group were ineligible after randomisation (eg, caesarean section, forceps delivery, short umbilical cord or nuchal cord). Mean weight change was 56 g (SD 47, 95% CI 50-63) for 197 babies in the introitus group compared with 53 g (45, 46-59) for 194 babies in the abdomen group, supporting non-inferiority of the two approaches (difference 3 g, 95% CI -5.8 to 12.8; p=0.45). We did not note any serious adverse events during the study.

INTERPRETATION:

Position of the newborn baby before cord clamping does not seem to affect volume of placental transfusion. Mothers could safely be allowed to hold their baby on their abdomen or chest. This change in practice might increase obstetric compliance with the procedure, enhance maternal-infant bonding, and decrease iron deficiency in infancy.

Eur J Pediatr. 2015 Mar 24. [Epub ahead of print]

Comparison of two types of intervention to enhance placental redistribution in term infants: randomized control trial.

Jaiswal P[1], Upadhyay A, Gothwal S, Singh D, Dubey K, Garg A, Vishnubhatala S.

Department of Pediatrics, LLRM Medical College, Meerut, India,

Abstract

The objective of the study was to compare the effect of umbilical cord milking (UCM) and delayed cord clamping (DCC) on hematological parameters (serum ferritin and hemoglobin) at 6 weeks of life in term neonates. It was a randomized controlled trail conducted at a teaching hospital in North India during August 2012 to August 2013. Babies born at >36 weeks of gestation were randomized in two groups, UCM and DCC (100 in each group). Umbilical cord milking was done after cutting and clamping the cord at 25 cm from the umbilicus. In DCC group, clamping was delayed by 60 to 90 s before cutting the cord. The baseline characteristics were comparable in the two groups. Mean serum ferritin (134.0 ng/ml [89.8]) and mean hemoglobin (11.0 gm/dl [2.4]) in umbilical cord milking group was comparable to mean serum ferritin (142.7 ng/ml [87.1]) and hemoglobin (11.3 gm/dl [2.6]) in DCC group at 6 weeks of age. There was no difference in hemodynamic status, cranial Doppler indices, and adverse neonatal outcomes among the two groups.

CONCLUSION:

In term neonates, the DCC and UCM had comparable effect on hematological parameters at 6 weeks of life. What is Known: • Delayed cord blood clamping improves certain hematologic parameters for neonates, which is potentially important in populations with high rates of neonatal and childhood anemia, but that delayed cord blood clamping may not be feasible in clinical situations when neonatal resuscitation is urgent. What is New: • There is no significant difference in ferritin and hemoglobin levels at 6 weeks among term, Indian neonates who had UCM and DCC and that this study may give support to the practice of UCM in term deliveries when DCC is not feasible.

BMC Pediatr. 2014 Jul 22;14:187. doi: 10.1186/1471-2431-14-187.

Effect of home-based counselling on newborn care practices in southern Tanzania one year after implementation: a cluster-randomised controlled trial.

Penfold S[1], Manzi F, Mkumbo E, Temu S, Jaribu J, Shamba DD, Mshinda H, Cousens S, Marchant T, Tanner M, Schellenberg D, Schellenberg JA.

London School of Hygiene and Tropical Medicine, Keppel Street, London, UK.

BACKGROUND:

In Sub-Saharan Africa over one million newborns die annually. We developed a sustainable and scalable home-based counselling intervention for delivery by community volunteers in rural southern Tanzania to improve newborn care practices and survival. Here we report the effect on newborn care practices one year after full implementation.

METHODS:

All 132 wards in the 6-district study area were randomised to intervention or comparison groups. Starting in 2010, in intervention areas trained volunteers made home visits during pregnancy and after childbirth to promote recommended newborn care practices including hygiene, breastfeeding and identification and extra care for low birth weight babies. In 2011, in a representative sample of 5,240 households, we asked women who had given birth in the previous year both about counselling visits and their childbirth and newborn care practices.

RESULTS:

Four of 14 newborn care practices were more commonly reported in intervention than comparison areas: delaying the baby's first bath by at least six hours (81% versus 68%, OR 2.0 (95% CI 1.2-3.4)), exclusive breastfeeding in the three days after birth (83% versus 71%, OR 1.9 (95% CI 1.3-2.9)), putting nothing on the cord (87% versus 70%, OR 2.8 (95% CI 1.7-4.6)), and, for home births, tying the cord with a clean thread (69% versus 39%, OR 3.4 (95% CI 1.5-7.5)). For other behaviours there was little evidence of differences in reported practices between intervention and comparison areas including childbirth in a health facility or with a skilled attendant, thermal care practices, breastfeeding within an hour of birth and, for home births, the birth attendant having clean hands, cutting the cord with a clean blade and birth preparedness activities.

CONCLUSIONS:

A home-based counselling strategy using volunteers and designed for scale-up can improve newborn care behaviours in rural communities of southern Tanzania. Further research is needed to evaluate if, and at what cost, these gains will lead to improved newborn survival.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4115472/pdf/1471-2431-14-187.pdf

BMC Pregnancy Childbirth. 2014 Sep 6;14:310. doi: 10.1186/1471-2393-14-310.

Seasonality of birth outcomes in rural Sarlahi District, Nepal: a population-based prospective cohort.

Hughes MM, Katz J[1], Mullany LC, Khatry SK, LeClerq SC, Darmstadt GL, Tielsch JM.

Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland USA.

BACKGROUND:

While seasonality of birth outcomes has been documented in a variety of settings, data from rural South Asia are lacking. We report a descriptive study of the seasonality of prematurity, low birth weight, small for gestational age, neonatal deaths, and stillbirths in the plains of Nepal.

METHODS:

Using data collected prospectively during a randomized controlled trial of neonatal skin and umbilical cord cleansing with chlorhexidine, we analyzed a cohort of 23,662 babies born between September 2002 and January 2006. Project workers collected data on birth outcomes at the infant's household. Supplemental data from other studies conducted at the same field site are presented to provide context. 95% confidence intervals were constructed around monthly estimates to examine statistical significance of findings.

RESULTS:

Month of birth was associated with higher risk for adverse outcomes (neonatal mortality, low birthweight, preterm, and small for gestational age), even when controlling for maternal characteristics. Infants had 87% (95% CI: 27 - 176%) increased risk of neonatal mortality when born in August, the high point, versus March, the low point.

CONCLUSION:

Seasonality of neonatal deaths, stillbirths, birth weight, gestational age, and small for gestational age were found in Nepal. Maternal factors, meteorological conditions, infectious diseases, and nutritional status may be associated with these adverse birth outcomes. Further research is needed to understand the causal mechanisms that explain the seasonality of adverse birth outcomes.

Eur J Pediatr. 2015 Feb;174(2):237-43. doi: 10.1007/s00431-014-2385-4. Epub 2014 Aug 3.

Role of prophylactic antibiotics in neonates born through meconium-stained amniotic fluid (MSAF)--a randomized controlled trial.

Goel A[1], Nangia S, Saili A, Garg A, Sharma S, Randhawa VS.

Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children Hospital, New Delhi, India,

Abstract

The objective of the study was to evaluate the effect of administering prophylactic antibiotics on the development of neonatal sepsis in term neonates born through meconium-stained amniotic fluid (MSAF). Two hundred and fifty eligible neonates were randomized to study group (Antibiotic group-receiving first-line antibiotics for 3 days) and control group (No Antibiotic group). Both groups were evaluated clinically and by laboratory parameters (sepsis screen and blood cultures) for development of sepsis. All neonates were monitored for respiratory, neurological, and other systemic complications and received supportive treatment according to standard management protocol of the unit. One hundred and twenty one neonates were randomized to 'Antibiotic' group and 129 to 'No Antibiotic' group. The overall incidence of suspect sepsis was 9.6 % in the study population with no significant difference between 'No Antibiotic' and 'Antibiotic' groups (10.8 vs. 8.2 %, p = 0.48, odds ratio (OR) 0.74, 95 % confidence interval (CI) 0.32-1.73). Incidence of culture-proven sepsis was also not significantly

different between the two groups (5.42 vs. 4.13 %, p = 0.63, OR 0.75, 95 % CI 0.23-2.43). The incidence of mortality, meconium aspiration syndrome, and other complications was comparable amongst the two groups.

CONCLUSION:

Routine antibiotic prophylaxis in neonates born through MSAF did not reduce the incidence of sepsis in this study population.

Health Policy Plan. 2014 Sep;29 Suppl 2:ii114-27. doi: 10.1093/heapol/czu080.

Evaluating the implementation of community volunteer assessment and referral of sick babies: lessons learned from the Ghana Newhints home visits cluster randomized controlled trial.

Ansah Manu A[1], ten Asbroek A[2], Soremekun S[2], Gyan T[2], Weobong B[2], Tawiah-Agyemang C[2], Danso S[2], Amenga-Etego S[2], Owusu-Agyei S[3], Hill Z[2], Kirkwood BR[2].

Kintampo Health Research Centre, Ghana Health Service, Kintampo, Brong Ahafo Region, Ghana, Department of Public Health, Academic Medical Centre, Amsterdam, The Netherlands, Department of Nutrition and Public Health Intervention Research, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK and Institute of Child Health, University College LondonUK Kintampo Health Research Centre, Ghana Health Service, Brong Ahafo Region, Ghana, Department of Public Health, Academic Medical Centre, Amsterdam, The Netherlands, Department of Nutrition and Public Health Intervention Research, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK and Institute of Child Health, University College London, London UK ; Kintampo Health Research Centre, Ghana Health Service, Ghana, Department of Public Health, Academic Medical Centre, Amsterdam, The Netherlands, Department of Nutrition and Public Health Intervention Research, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK and Institute of Child Health, University College London UK.

Abstract

A World Health Organization (WHO)/United Nations Children's Fund (UNICEF) (2009) joint statement recommended home visits by community-based agents as a strategy to improve newborn survival, based on promising results from Asia. This article presents detailed evaluation of community volunteer assessment and referral implemented within the Ghana Newhints home visits cluster-Randomized Controlled Trial (RCT). It highlights the lessons learned to inform implementation/scale-up of this model in similar settings. The evaluation used a conceptual framework adopted for increasing access to care for sick newborns and involves three main steps, each with a specific goal and key requirements to achieving this. These steps are: sick newborns are identified within communities and referred; families comply with referrals and referred babies receive appropriate management at health facilities. Evaluation data included interviews with 4006 recently delivered mothers; records on 759 directly observed volunteer assessments and 52 validation of supervisors' assessments; newborn care quality assessment in 86 health facilities and in-depth interviews (IDIs) with 55 mothers, 21 volunteers and 15 health professionals. Assessment accuracy of volunteers against supervisors and physician was assessed using Kappa (agreement coefficient). IDIs were analysed by generating and indexing into themes, and exploring relationships between themes and their contextual

interpretations. This evaluation demonstrated that identifying, understanding and implementing the key requirements for success in each step of volunteer assessment and referrals was pivotal to success. In Newhints, volunteers (CBSVs) were trusted by families, their visits were acceptable and they engaged mothers/families in decisions, resulting in unprecedented 86% referral compliance and increased (55-77%) care seeking for sick newborns. Poor facility care quality, characterized by poor health worker attitudes, limited the mortality reduction. The important implication for future implementation of home visits in similar settings is that, with 100% specificity but 80% sensitivity of referral decisions, volunteers might miss some danger signs but if successful implementation must translate into mortality reductions, concurrent improvement in facility newborn care quality is imperative.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4202912/pdf/czu080.pdf

J Paediatr Child Health. 2014 Sep;50(9):674-9. doi: 10.1111/jpc.12611. Epub 2014 Jun 2.

Home-use icterometry in neonatal hyperbilirubinaemia: Cluster-randomised controlled trial in Vietnam.

Luu MN[1], Le LT, Tran BH, Duong TK, Nguyen HT, Le VT, Partridge JC.

Department of Medicine, University of California, San Francisco, California, United States.

AIM:

To determine whether home-use icterometry improves parental recognition of neonatal jaundice, early care seeking and treatment to minimize risks of bilirubin encephalopathy.

METHODS:

Cluster-randomised controlled trial of community-level icterometry used at home by mothers in Chi Linh, Vietnam. Rural health-care workers identified and enrolled term newborns. Post-partum mothers received jaundice education and icterometry instructions and were cluster-randomised by commune. Cases received icterometers (icterometer group (IG)) and controls did not (control group (CG)). Subjects received mobile telephone calls from post-natal days 2-7 to determine maternal recognition by visual inspection and icterometer detection of jaundice (≥ 3.0 on five-point scale). Mothers without telephones, premature newborns (<35 weeks) or newborns hospitalised >5 days were excluded.

RESULTS:

Three hundred fifty-two subjects were enrolled (183 IG and 169 CG), of whom 11 (3.4%) were lost to telephone follow-up. Jaundice was recognised and/or detected in 94 (27%) of all newborns. Icterometry helped 11 mothers (6%) detect neonatal jaundice that was not visually recognised by IG mothers. Detection by IG mothers was not statistically greater than CG mothers (P = 0.09). Follow-up care seeking was 8% in both groups (P = 0.2), and 11% of jaundiced newborns received treatment (9% IG vs. 16% CG, P = 0.3). Newborns who received care had bilirubin measurements that averaged 257 μmol/L IG vs. 322 μmol/L CG (P = 0.3). There were no deaths.

CONCLUSIONS:

In this pilot study, home-use icterometry may help improve parental detection of jaundice in rural Vietnam. However, larger studies are necessary to determine the changes in recognition, care seeking and treatment.

Child Care Health Dev. 2015 Jan;41(1):52-6. doi: 10.1111/cch.12166. Epub 2014 Jun 9.

A randomized controlled trial of burping for the prevention of colic and regurgitation in healthy infants.

Kaur R[1], Bharti B, Saini SK.

National Institute of Nursing Education, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

BACKGROUND:

Efficacy of burping in lowering colic and regurgitation episodes in healthy term babies lacks evidence in literature.

METHODS:

We conducted a randomized controlled trial to compare efficacy of burping versus no-burping in 71 mother-baby dyads in community setting. Primary outcome was reduction in event rates of colic and regurgitation episodes over 3 months.

RESULTS:

Baseline characteristics were similar in two groups. Difference in incidence rates of colic between the control and burping group was 1.57 episodes/infant/100 weeks [95% confidence interval (CI): -0.63 to 3.76]. There was statistically no significant reduction in colic episodes between burping and non-burping study subjects during 3 months of follow-up (adjusted relative risk 0.64; 95% CI: 0.22-1.86, P-value 0.41). Incidence rate difference of regurgitation episodes/infant/week between burping and control group was 4.36 (95% CI: 4.04 to 4.69) and there was statistically significant increase in burping group (adjusted relative risk 2.05; 95% CI: 1.92-2.18, P-value < 0.0001).

CONCLUSIONS:

Although burping is a rite of passage, our study showed that burping did not significantly lower colic events and there was significant increase in regurgitation episodes in healthy term infants up to 3 months of follow-up.

J Spec Pediatr Nurs. 2014 Jul;19(3):247-56. doi: 10.1111/jspn.12076. Epub 2014 Mar 18.

Learning and adherence to baby massage after two teaching strategies.

Cruz CM[1], Caromano FA, Gonçalves LL, Machado TG, Voos MC.

Universidade de São Paulo, São Paulo, SP, Brazil.

PURPOSE:

Little is known about learning/adherence after different baby massage teaching strategies. We compared the learning/adherence after two strategies.

DESIGN AND METHODS:

Twenty mothers from the group manual-course (GMC) and 20 from the group manual-orientations (GMO) received a booklet. GMC participated in a course during the third trimester.

GMO received verbal instructions during the postpartum hospital stay. Multiple-choice and practical tests assessed learning (GMC: performing strokes on a doll; GMO: on the baby). Adherence was measured 3 months after childbirth.

RESULTS:

No differences were found between the groups in learning/adherence.

PRACTICE IMPLICATIONS:

Both teaching strategies showed similar and positive results.

Low birth weight and prematurity

Lancet. 2015 Feb 14;385(9968):629-39. doi: 10.1016/S0140-6736(14)61651-2. Epub 2014 Oct 15.

A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial.

Althabe F[1], Belizán JM[2], McClure EM[3], Hemingway-Foday J[3], Berrueta M[2], Mazzoni A[2], Ciganda A[4], Goudar SS[5], Kodkany BS[5], Mahantshetti NS[5], Dhaded SM[5], Katageri GM[6], Metgud MC[5], Joshi AM[5], Bellad MB[5], Honnungar NV[5], Derman RJ[7], Saleem S[8], Pasha O[8], Ali S[8], Hasnain F[8], Goldenberg RL[9], Esamai F[10], Nyongesa P[10], Ayunga S[10], Liechty EA[11], Garces AL[12], Figueroa L[13], Hambidge KM[14], Krebs NF[14], Patel A[15], Bhandarkar A[16], Waikar M[16], Hibberd PL[17], Chomba E[18], Carlo WA[19], Mwiche A[18], Chiwila M[20], Manasyan A[19], Pineda S[13], Meleth S[3], Thorsten V[3], Stolka K[3], Wallace DD[3], Koso-Thomas M[21], Jobe AH[22], Buekens PM[23].

Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina.; Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina.RTI International, Durham, NC, USA.; Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina; UNICEM, Montevideo, Uruguay.; Women's and Children's Health Research Unit, KLE University's Jawaharlal Nehru Medical College, Belgaum, Karnataka, India.; S Nijalingappa Medical College, Bagalkot, Karnataka, India.; Department of Obstetrics and Gynecology, Christiana Health Care Services, Newark, DE, USA.; Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan.; Department of Obstetrics and Gynecology, Columbia University, New York, NY, USA.; Moi University School of Medicine, Eldoret, Kenya.; School of Medicine, Indiana University, Indianapolis, IN, USA; Fundación para la Alimentación y Nutrición de Centro América y Panamá, Guatemala City, Guatemala; Francisco Marroquin University, Guatemala City, Guatemala.; Fundación para la Alimentación y Nutrición de Centro América y Panamá, Guatemala City, Guatemala.; University of Colorado School of Medicine, Denver, CO, USA.; Lata Medical Research Foundation, Nagpur, India; Indira Gandhi Government Medical College, Nagpur, India.; Lata Medical Research Foundation, Nagpur, India.; Massachusetts General Hospital, Boston, MA, USA.; University Teaching Hospital, Lusaka, Zambia.; University of Alabama at Birmingham, Birmingham, AL, USA.; Centre for Infectious Disease Zambia, Lusaka, Zambia.; Eunice Kennedy Shriver

National Institute of Child Health and Human Development, Bethesda, MD, USA.; Cincinnati Children's Hospital, Cincinnati, OH, USA.; Tulane School of Public Health and Tropical Medicine, New Orleans, LA, USA.

BACKGROUND:

Antenatal corticosteroids for pregnant women at risk of preterm birth are among the most effective hospital-based interventions to reduce neonatal mortality. We aimed to assess the feasibility, effectiveness, and safety of a multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels of health care in low-income and middle-income countries.

METHODS:

In this 18-month, cluster-randomised trial, we randomly assigned (1:1) rural and semi-urban clusters within six countries (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia) to standard care or a multifaceted intervention including components to improve identification of women at risk of preterm birth and to facilitate appropriate use of antenatal corticosteroids. The primary outcome was 28-day neonatal mortality among infants less than the 5th percentile for birthweight (a proxy for preterm birth) across the clusters. Use of antenatal corticosteroids and suspected maternal infection were additional main outcomes. This trial is registered with ClinicalTrials.gov, number NCT01084096.

FINDINGS:

The ACT trial took place between October, 2011, and March, 2014 (start dates varied by site). 51 intervention clusters with 47,394 livebirths (2520 [5%] less than 5th percentile for birthweight) and 50 control clusters with 50,743 livebirths (2258 [4%] less than 5th percentile) completed follow-up. 1052 (45%) of 2327 women in intervention clusters who delivered less-than-5th-percentile infants received antenatal corticosteroids, compared with 215 (10%) of 2062 in control clusters (p<0·0001). Among the less-than-5th-percentile infants, 28-day neonatal mortality was 225 per 1000 livebirths for the intervention group and 232 per 1000 livebirths for the control group (relative risk [RR] 0·96, 95% CI 0·87-1·06, p=0·65) and suspected maternal infection was reported in 236 (10%) of 2361 women in the intervention group and 133 (6%) of 2094 in the control group (odds ratio [OR] 1·67, 1·33-2·09, p<0·0001). Among the whole population, 28-day neonatal mortality was 27·4 per 1000 livebirths for the intervention group and 23·9 per 1000 livebirths for the control group (RR 1·12, 1·02-1·22, p=0·0127) and suspected maternal infection was reported in 1207 (3%) of 48,219 women in the intervention group and 867 (2%) of 51,523 in the control group (OR 1·45, 1·33-1·58, p<0·0001).

INTERPRETATION:

Despite increased use of antenatal corticosteroids in low-birthweight infants in the intervention groups, neonatal mortality did not decrease in this group, and increased in the population overall. For every 1000 women exposed to this strategy, an excess of 3·5 neonatal deaths occurred, and the risk of maternal infection seems to have been increased.

J Pediatr. 2015 Mar;166(3):545-51.e1. doi: 10.1016/j.jpeds.2014.12.004. Epub 2015 Jan 13.

The propre-save study: effects of probiotics and prebiotics alone or combined on necrotizing enterocolitis in very low birth weight infants.

Dilli D[1], Aydin B[2], Fettah ND[2], Özyazıcı E[2], Beken S[2], Zenciroğlu A[2], Okumuş N[2], Özyurt BM[3], İpek MŞ[3], Akdağ A[4], Turan Ö[5], Bozdağ Ş[6].

Department of Neonatology, Dr Sami Ulus Maternity and Children Research and Training Hospital, Ankara, Turkey. ; [3]Department of Neonatology, Diyarbakir Maternity and Children Hospital, Diyarbakır, Turkey.; Department of Neonatology, Bursa Şevket Yılmaz Training and Research Hospital, Bursa, Turkey.; Department of Neonatology, Okmeydanı Education and Research Hospital, İstanbul, Turkey.; Department of Neonatology, Ümraniye Training and Research Hospital, İstanbul, Turkey.

OBJECTIVE:

To test the efficacy of probiotic and prebiotic, alone or combined (synbiotic), on the prevention of necrotizing enterocolitis (NEC) in very low birth weight (VLBW) infants.

STUDY DESIGN:

A prospective, randomized, controlled trial was conducted at 5 neonatal intensive care units in Turkey. VLBW infants (n = 400) were assigned to a control group and 3 study groups that were given probiotic (Bifidobacterium lactis), prebiotic (inulin), or synbiotic (Bifidobacterium lactis plus inulin) added to breastmilk or formula for a maximum of 8 weeks before discharge or death. The primary outcome was NEC (Bell stage ≥2).

RESULTS:

The rate of NEC was lower in probiotic (2.0%) and synbiotic (4.0%) groups compared with prebiotic (12.0%) and placebo (18.0%) groups (P < .001). The times to reach full enteral feeding were faster (P < .001), the rates of clinical nosocomial sepsis were lower (P = .004), stays in the neonatal intensive care unit were shorter, (P = .002), and mortality rates were lower (P = .003) for infants receiving probiotics, prebiotics, or synbiotic than controls. The use of antenatal steroid (OR 0.5, 95% CI 0.3-0.9) and postnatal probiotic (alone or in synbiotic) (OR 0.5, 95% CI 0.2-0.8) decreased the risk of NEC, and maternal antibiotic exposure increased this risk (OR 1.9, 95% CI 1.1-3.6).

CONCLUSIONS:

In VLBW infants, probiotic (Bifidobacterium lactis) and synbiotic (Bifidobacterium lactis plus inulin) but not prebiotic (inulin) alone decrease NEC.

J Trop Pediatr. 2015 Apr;61(2):135-8. doi: 10.1093/tropej/fmu073. Epub 2014 Dec 25.

Efficacy of expressed breast milk in reducing pain during ROP screening--a randomized controlled trial.

Rosali L[1], Nesargi S[2], Mathew S[3], Vasu U[4], Rao SP[5], Bhat S[5].

Department of Child Health, St. Johns College of Nursing, Bangalore, India.; Department of Neonatology, St. John's Medical College Hospital, Bangalore, India ; Department of Childhealth, St. Johns College of Nursing, Bangalore, India.; Department of Ophthalmology, St. John's Medical College Hospital, Bangalore, India.; Department of Neonatology, St. John's Medical College Hospital, Bangalore, India.

OBJECTIVE:

To assess the effectiveness of expressed breast milk (EBM) on neonatal pain during screening for retinopathy of prematurity (ROP).

METHODS:

Neonates who were on oral feeds undergoing ROP screening were included. Babies were randomized into intervention group (EBM + Standard practice) and control group. The standard practice is proparacaine, nesting and swaddling. Pain was assessed by PIPP scale, during and at 1 and 5 min after the procedure by the principal investigator who was blinded.

RESULTS:

The groups were similar in baseline characteristics. The group receiving EBM had significantly lower PIPP scores during the procedure 12.7 ± 1.69 compared to the control group 15.5 ± 1.78 ($p < 0.05$). The beneficial effect persisted at 1 min and 5 min after the procedure 6.20 ± 1.9 vs. 12.4 ± 2.54 ($p \leq 0.05$) at 1 min; 3.2 ± 1.5 and 6.85 ± 2.4 ($p < 0.05$) at 5 min.

CONCLUSION:

Oral EBM significantly reduces pain during and after ROP screening.

Neonatal infection

Lancet. 2015 May 2;385(9979):1767-76. doi: 10.1016/S0140-6736(14)62284-4. Epub 2015 Apr 1.

Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial.

African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A[1], Lokangaka A[1], Ngaima S[1], Engmann C[2], Esamai F[3], Gisore P[4], Ayede AI[5], Falade AG[5], Adejuyigbe EA[6], Anyabolu CH[6], Wammanda RD[7], Ejembi CL[8], Ogala WN[7], Gram L[9], Cousens S[9].

Department of Community Health, Kinshasa School of Public Health, Kinshasa, DR Congo.; Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina,NC, USA.; Department of Child Health and Paediatrics, School of Medicine, Moi University, Eldoret, Kenya.; Department of Child Health and Paediatrics, School of Medicine, Moi University, Eldoret, Kenya.; Department of Paediatrics, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria.; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria.; Department of Paediatrics, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria.; Department of Community Medicine, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria.; Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK.

BACKGROUND:

WHO recommends hospital-based treatment for young infants aged 0-59 days with clinical signs of possible serious bacterial infection, but most families in resource-poor settings cannot accept referral. We aimed to assess whether use of simplified antibiotic regimens to treat young infants with clinical signs of severe infection was as efficacious as an injectable procaine benzylpenicillin-gentamicin combination for 7 days for situations in which hospital referral was not possible.

METHODS:

In a multisite open-label equivalence trial in DR Congo, Kenya, and Nigeria, community health workers visited all newborn babies at home, identifying and referring unwell young infants to a study nurse. We stratified young infants with clinical signs of severe infection whose parents did not accept referral to hospital by age (0-6 days and 7-59 days), and randomly assigned each individual within these strata to receive one of the four treatment regimens. Randomisation was stratified by age group of infants. An age-stratified randomisation scheme with block size of eight was computer-generated off-site at WHO. The outcome assessor was masked. We randomly allocated infants to receive injectable procaine benzylpenicillin-gentamicin for 7 days (group A, reference group); injectable gentamicin and oral amoxicillin for 7 days (group B); injectable procaine benzylpenicillin-gentamicin for 2 days, then oral amoxicillin for 5 days (group C); or injectable gentamicin for 2 days and oral amoxicillin for 7 days (group D). Trained health professionals gave daily injections and the first dose of oral amoxicillin. Our primary outcome was treatment failure by day 8 after enrolment, defined as clinical deterioration, development of a serious adverse event (including death), no improvement by day 4, or not cured by day 8. Independent outcome assessors, who did not know the infant's treatment regimen, assessed study outcomes on days 4, 8, 11, and 15. Primary analysis was per protocol. We used a prespecified similarity margin of 5% to assess equivalence between regimens. This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000286044.

FINDINGS:

In Kenya and Nigeria, we started enrolment on April 4, 2011, and we enrolled the necessary number of young infants aged 7 days or older from Oct 17, 2011, to April 30, 2012. At these sites, we continued to enrol infants younger than 7 days until March 29, 2013. In DR Congo, we started enrolment on Sept 17, 2012, and continued until June 28, 2013. We randomly assigned 3564 young infants to either group A (n=894), group B (n=884), group C (n=896), or group D (n=890). We excluded 200 randomly assigned infants, who did not fulfil the predefined criteria of adherence to treatment and adequate follow-up. In the per-protocol analysis, 828 infants were included in group A, 826 in group B, 862 in group C, and 848 in group D. 67 (8%) infants failed treatment in group A compared with 51 (6%) infants in group B (risk difference -1·9%, 95% CI -4·4 to 0·1), 65 (8%) in group C (-0·6%, -3·1 to 2·0), and 46 (5%) in group D (-2·7%, -5·1 to 0·3). Treatment failure in groups B, C, and D was within the similarity margin compared with group A. During the 15 days after random allocation, 12 (1%) infants died in group A, compared with ten (1%) infants in group B, 20 (2%) infants in group C, and 11 (1%) infants in group D. An infant in group A had a serious adverse event other than death (injection abscess).

INTERPRETATION:

The three simplified regimens were as effective as injectable procaine benzylpenicillin-gentamicin for 7 days on an outpatient basis in young infants with clinical signs of severe infection, without signs of critical illness, and whose caregivers did not accept referral for hospital admission.

Lancet. 2015 May 2;385(9979):1758-66. doi: 10.1016/S0140-6736(14)62285-6. Epub 2015 Apr 1.

Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with fast breathing when referral is not possible: a randomised, open-label, equivalence trial.

African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A[1], Lokangaka A[1], Ngaima S[1], Engmann C[2], Esamai F[3], Gisore P[3], Ayede AI[4], Falade AG[4], Adejuyigbe EA[5], Anyabolu CH[6], Wammanda RD[7], Ejembi CL[8], Ogala WN[7], Gram L[9], Cousens S[9].

Department of Community Health, Kinshasa School of Public Health, Kinshasa, DR Congo.; Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina, Chapel Hill, NC, USA.; Department of Child Health and Paediatrics, School of Medicine, Moi University, Eldoret, Kenya.

Department of Paediatrics, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria.; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria. ; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria.; Department of Paediatrics, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria.; Department of Community Medicine, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria.; Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK.

BACKGROUND:

WHO recommends referral to hospital for possible serious bacterial infection in young infants aged 0-59 days. We aimed to assess whether oral amoxicillin treatment for fast breathing, in the absence of other signs, is as efficacious as the combination of injectable procaine benzylpenicillin-gentamicin.

METHODS:

In a randomised, open-label, equivalence trial at five sites in DR Congo, Kenya, and Nigeria, community health workers followed up all births in the community, identified unwell young infants, and referred them to study nurses. We randomly assigned infants with fast breathing as a single sign of illness or possible serious bacterial infection, whose parents did not accept referral to hospital, to receive either injectable procaine benzylpenicillin-gentamicin once per day or oral amoxicillin treatment twice per day for 7 days. A person who was off-site generated randomisation lists using computer software. Trained health professionals gave injections, but outcome assessors were masked to group allocations. The primary outcome was treatment failure by day 8 after enrolment, defined as clinical deterioration, development of a serious adverse event including death, persistence of fast breathing on day 4, or recurrence up to day 8. The primary analysis was per protocol and we used a prespecified similarity margin of 5% to assess equivalence between regimens. This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000286044.

FINDINGS:

From April 4, 2011, to March 29, 2013, we enrolled 2333 infants aged 0-59 days with fast breathing as the only sign of possible serious bacterial infection at the five study sites. We assigned 1170 infants to receive injectable procaine benzylpenicillin-gentamicin and 1163 infants to receive oral amoxicillin. In the per-protocol analysis, from which 137 infants were

excluded, we included 1061 (91%) infants who fulfilled predefined criteria of adherence to treatment and adequate follow-up in the injectable procaine benzylpenicillin-gentamicin group and 1145 (98%) infants in the oral amoxicillin group. In the procaine benzylpenicillin-gentamicin group, 234 infants (22%) failed treatment, compared with 221 (19%) infants in the oral amoxicillin group (risk difference -2·6%, 95% CI -6·0 to 0·8). Four infants died within 15 days of follow-up in each group. We detected no drug-related serious adverse events.

INTERPRETATION:

Young infants with fast breathing alone can be effectively treated with oral amoxicillin on an outpatient basis when referral to a hospital is not possible.

Nutrition, micronutrients and breast feeding

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Micronutients, multivitamins and food fortification

J Nutr. 2014 Dec;144(12):2059-65. doi: 10.3945/jn.114.201673. Epub 2014 Oct 1.

Multiple micronutrient supplementation transiently ameliorates environmental enteropathy in Malawian children aged 12-35 months in a randomized controlled clinical trial.

Smith HE[1], Ryan KN[1], Stephenson KB[1], Westcott C[1], Thakwalakwa C[2], Maleta K[2], Cheng JY[3], Brenna JT[3], Shulman RJ[4], Trehan I[5], Manary MJ[6].

Department of Pediatrics, Washington University, St. Louis, MO; College of Medicine, University of Malawi, Blantyre, Malawi; Division of Nutritional Sciences, Cornell University, Ithaca, NY; and.; Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX.; Department of Pediatrics, Washington University, St. Louis, MO; College of Medicine, University of Malawi, Blantyre, Malawi; Department of Pediatrics, Washington University, St. Louis, MO; College of Medicine, University of Malawi, Blantyre, Malawi; Children's Nutrition Research Center, Baylor College of Medicine, Houston,

BACKGROUND:

Environmental enteropathy (EE) is subclinical, diffuse villous atrophy characterized by T cell infiltration of the small intestinal mucosa associated with nutrient malabsorption and stunting. EE is assessed by the lactulose:mannitol (L:M) test, whereby nonmetabolized sugars are ingested and quantified in the urine. Multiple micronutrient (MN) deficiency morphologically mimics EE, and ω-3 (n-3) polyunsaturated fatty acids reduce mucosal inflammation in Crohn disease.

OBJECTIVE:

We tested the hypothesis that supplementary MNs, with or without fish oil (FO), would improve L:M in rural Malawian children aged 1-3 y compared with a control (C) group receiving a placebo.

METHODS:

The MNs and FO provided the Recommended Dietary Intake for 26 vitamins, minerals, eicosapentaenoic acid, and docosahexaenoic acid. This was a 3-arm, randomized, double-blind, placebo-controlled clinical trial, with the primary outcomes being the change in L:M (ΔL:M) after 12 and 24 wk of supplementation. Comparisons were made for ΔL:M after 12 and 24 wk within each group by using a Wilcoxon matched pairs signed rank test, because the data are not normally distributed.

RESULTS:

A total of 230 children had specimens adequate for analysis; all had an abnormal baseline L:M, defined as >0.10. After 12 wk, children who received MNs + FO had a ΔL:M [mean (95% CI)] of -0.10 (-0.04, -0.15; P = 0.001), and children receiving only MNs had ΔL:M of -0.12 (-0.03, -0.21; P = 0.002). After 24 wk, children who received MNs + FO had a ΔL:M of -0.09 (-0.03, -0.15; P = 0.001); children receiving only MNs had a ΔL:M of -0.11 (-0.02, -0.20; P = 0.001), and the C group had ΔL:M of -0.07 (0.02, -0.16); P = 0.002). Linear growth was similar in all groups, ~4.3 cm over 24 wk.

CONCLUSION:

Although the effect was modest, these data suggest MNs can transiently ameliorate EE in rural African children. The trial was registered at clinicaltrials.gov as NCT01593033.

J Nutr. 2014 Nov;144(11):1803-10. doi: 10.3945/jn.114.193094. Epub 2014 Aug 20.

A 22-element micronutrient powder benefits language but not cognition in Bangladeshi full-term low-birth-weight children.

Singla DR[1], Shafique S[2], Zlotkin SH[2], Aboud FE[2].

Department of Psychology, McGill University, Montréal, QC, Canada ; Department of Psychology, McGill University, Montréal, QC, Canada.

BACKGROUND:

Low-birth-weight children are known to be at risk of both anemia and cognitive/language deficits in their early years.

OBJECTIVE:

The aim of the current study was to examine the effects of a 22-element multiple micronutrient powder (MNP) on the cognitive and language development of full-term low-birth-weight (LBW-T) children in Bangladesh.

METHODS:

The current study was a follow-up of children who were enrolled in a randomized cluster trial at 7-12 mo of age. Children in 12 intervention clusters (communities) were administered a daily 22-element MNP sachet with their food for 5 mo, and both intervention and control groups (also 12 clusters) received nutrition, health, and hygiene education. The current study involved the assessment of children at 16-22 mo of age (22-element MNP group: n = 96; control group: n = 82) on 3 subtests of the Bayley Scales of Infant and Toddler Development III test to measure cognitive, receptive language, and expressive language development.

RESULTS:

There was a significant effect of the 22-element MNP on children's expressive language scores (d = 0.39), and stunting moderated the effect on receptive language scores; there was no effect on cognitive development (d = 0.08).

CONCLUSION:

An MNP may thus offer one feasible solution to improve language development of LBW-T children in low-resource community settings.

Ann N Y Acad Sci. 2014 Sep;1324:48-54. doi: 10.1111/nyas.12506. Epub 2014 Aug 25.

Organoleptic qualities and acceptability of fortified rice in two Southeast Asian countries.

Khanh Van T[1], Burja K, Thuy Nga T, Kong K, Berger J, Gardner M, Dijkhuizen MA, Hop le T, Tuyen le D, Wieringa FT.

National Institute of Nutrition, Ministry of Health, Hanoi, Vietnam.

Abstract

Fortified rice has the potential to improve the micronutrients status of vulnerable populations. However, fortified rice has to have acceptable organoleptic--the sensory properties of a particular food--qualities. Few data exist on the acceptability of fortified rice in Asia. To assess the acceptability of two types of fortified rice (cold and hot extruded) in Vietnam and Cambodia, triangle tests were conducted in Vietnam (53 women) and Cambodia (258 adults), testing fortified rice against conventional rice, with participants being asked to score the organoleptic qualities. In addition, Cambodian schoolchildren (n = 1700) were given conventional rice and two types of fortified rice for two week periods as part of a World Food Program school meal program, with intake monitored. Fortified rice differed significantly in organoleptic qualities from conventional rice, with most subjects correctly identifying fortified rice ($P < 0.001$). However, fortified rice was found to be highly acceptable in both countries. In Cambodia, schoolchildren consuming fortified rice had higher intakes than when consuming conventional rice (176 g/child/day and 168 g/child/day, respectively; $P < 0.05$). This study shows that fortified rice is acceptable in two countries in Southeast Asia. However, specific information is needed to explain the organoleptic qualities of fortified rice as perceived by end-users.

Am J Clin Nutr. 2015 Apr;101(4):742-51. doi: 10.3945/ajcn.114.084889. Epub 2015 Jan 28.

Effects of animal source food and micronutrient fortification in complementary food products on body composition, iron status, and linear growth: a randomized trial in Cambodia.

Skau JK[1], Touch B[1], Chhoun C[1], Chea M[1], Unni US[1], Makurat J[1], Filteau S[1], Wieringa FT[1], Dijkhuizen MA[1], Ritz C[1], Wells JC[1], Berger J[1], Friis H[1], Michaelsen KF[1], Roos N[1].

From the Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark (JKHS, MD, CR, HF, KFM, and NR); Inland Fisheries Research and Development Institute, Phnom Penh, Cambodia (BT); Department of Fisheries Post-harvest Technologies and Quality Control, Fishery Administration, Ministry of Agriculture, Forestry and Fisheries, Phnom Penh, Cambodia (CC); National Nutrition Programme, Maternal and Child Health Centre, Ministry of Health, Phnom Penh, Cambodia (MC); Institute of Nutritional Sciences, Justus Liebig University, Giessen, Germany (JM); Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom (SF); Childhood Nutrition Research Centre, UCL Institute of Child Health, London, United Kingdom (JW); St. John's Research Institute, Bangalore, India (USU); and Institut de Recherche pour le Développement (IRD), Montpellier, France (FW and JB).

BACKGROUND:

Poor nutritional quality of complementary foods often limits growth. Animal source foods, such as milk or meat, are often unaffordable. Local affordable alternatives are needed.

OBJECTIVE:

We evaluate the efficacy of 2 newly developed, rice-based complementary food products: WinFood (WF) with small fish and edible spiders and WinFood-Lite (WF-L) fortified with small fish, against 2 existing fortified corn-soy blend products, CSB+ (purely plant based) and CSB++ (8% dried skimmed milk).

DESIGN:

In total, 419 infants aged 6 mo were enrolled in this randomized, single-blinded study for 9 mo, designed primarily to assess increments in fat-free mass by a deuterium dilution technique and change in plasma ferritin and soluble transferrin receptor. Secondary endpoints were changes in anthropometric variables, including knee-heel length. Data were analyzed by the intention-to-treat approach.

RESULTS:

There was no difference in fat-free mass increment in WF or WF-L compared with CSB+ [WF: +0.04 kg (95% CI: -0.20, 0.28 kg); WF-L: +0.14 kg (95% CI: -0.10, 0.38 kg)] or CSB++ [WF: -0.03 kg (95% CI: -0.27, 0.21 kg); WF-L: +0.07 kg (95% CI: -0.18, 0.31 kg)] and no effect on iron status. The 1.7-mm (95% CI: -0.1, 3.5 mm) greater increase in knee-heel length in WF-L than in CSB+ was not significant.

CONCLUSIONS:

No difference was found between the locally produced products (WF and WF-L) and the CSBs. Micronutrient fortification may be necessary, and small fish may be an affordable alternative to milk to improve complementary foods. The dietary role of edible spiders needs to be further explored. This trial was registered at controlled-trials.com as ISRCTN19918531.

Pediatrics. 2015 Apr;135(4):e918-26. doi: 10.1542/peds.2014-1848.

Vitamin B-12, folic acid, and growth in 6- to 30-month-old children: a randomized controlled trial.

Strand TA[1], Taneja S[2], Kumar T[3], Manger MS[4], Refsum H[5], Yajnik CS[6], Bhandari N[7].

Division for Medical Services, Innlandet Hospital Trust, Lillehammer, Norway; Centre for International Health, University of Bergen, Bergen, Norway; Society for Applied Studies, New Delhi, India; Society for Essential Health Action and Training, New Delhi, India; Centre for International Health, University of Bergen, Bergen, Norway; Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; Department of Pharmacology, University of Oxford, Oxford, United Kingdom; Diabetes Unit, King Edward Memorial Hospital, Pune, Maharashtra, India.; Society for Applied Studies, New Delhi, India;

BACKGROUND:

Folate and vitamin B-12 are important for growth. Many children in low- and middle-income countries have inadequate intakes of these nutrients.

METHODS:

We undertook a randomized, placebo controlled double-blind trial in 1000 North Indian children, 6 to 35 months of age, providing twice the recommended daily allowance of folic acid and/or vitamin B-12, or placebo, daily for 6 months. By using a factorial design, we allocated children in a 1:1:1:1 ratio in blocks of 16. We measured the effect of giving vitamin B-12, folic acid, or the combination of both on linear and ponderal growth. We also identified predictors for growth in multiple linear regression models and effect modifiers for the effect of folic acid or vitamin B-12 supplementation on growth.

RESULTS:

The overall effect of either of the vitamins was significant only for weight; children who received vitamin B-12 increased their mean weight-for-age z scores by 0.07 (95% confidence interval: 0.01 to 0.13). Weight-for-age z scores and height-for-age z scores increased significantly after vitamin B-12 supplementation in wasted, underweight, and stunted children. These subgrouping variables significantly modified the effect of vitamin B-12 on growth. Vitamin B-12 status at baseline predicted linear and ponderal growth in children not receiving vitamin B-12 supplements but not in those who did (P-interaction < .001).

CONCLUSIONS:

We provide evidence that poor vitamin B-12 status contributes to poor growth. We recommend studies with larger doses and longer follow-up to confirm our findings.

Clin Nutr. 2015 Feb 21. pii: S0261-5614(15)00044-8. doi: 10.1016/j.clnu.2015.02.001. [Epub ahead of print]

The effects of regular consumption of a multiple micronutrient fortified milk beverage on the micronutrient status of school children and on their mental and physical performance.

Kuriyan R[1], Thankachan P[2], Selvam S[2], Pauline M[2], Srinivasan K[2], Kamath-Jha S[3], Vinoy S[4], Misra S[5], Finnegan Y[6], Kurpad AV[2].

Division of Nutrition, St. John's Research Institute, India. [2]Division of Nutrition, St. John's Research Institute, India.; Mondelez International R&D, Nutrition Research, Glenview, IL, USA.; Mondelez International R&D, Nutrition Research, Saclay, France.; Mondelez

International R&D, Product Development Beverages, Thane, Maharashtra, India.; Kraft Foods Global, Inc, Glenview, IL, USA.

Abstract

Multiple micronutrient deficiencies exist in school going children in India and bridging the gap between nutrient intake and requirements is an effective way to combat the deficiencies. This study aimed to test the effect of a multi-micronutrient fortified malt and cocoa based milk beverage on the micronutrient status, cognition, physical performance and nutritional deficiencies of 7-10 years old south Indian children. A randomized, double blind placebo controlled study design was used with normal healthy children from low to middle income families, aged 7-10 years randomly assigned to receive either a multi-micronutrient fortified or an unfortified milk based control drink. The drinks were provided 6 days/week for 5 months. Assessments included anthropometry, blood biochemistry, physical performance and cognition at baseline and endline. The baseline characteristics of the study groups were similar. The changes in body weight and height were similar between the groups at the end of the study. Levels of vitamin B12, red cell folate and vitamin B2 significantly improved in the intervention group, while vitamin D, selenium and body iron showed no difference. The Hemoglobin (Hb) and serum ferritin levels of the control group decreased at endline, while those in the intervention group maintained their levels. The serum transferrin receptor levels increased in both the groups. The prevalence of iron deficiency and Vitamin B2 deficiency were significantly lower in the intervention group at endline. Overall improvement in cognitive and physical performance was seen in both the groups at endline, with no significant differences between the groups. The micronutrient fortified milk based drink was efficacious in improving the micronutrient status of Vitamin B2, Vitamin B12 and red cell folate and in preventing a decline in Hb level compared to an unfortified milk based drink. It also reduced anemia and the risk of deficiencies of iron, and B12, in apparently healthy children. ClinicalTrials.gov IdentifierNCT01415557. Clinical Trial RegistryIndia - REF/2012/12/004332.

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

J Nutr. 2014 Nov;144(11):1818-25. doi: 10.3945/jn.114.199547. Epub 2014 Sep 3.

Dietary diversity at 6 months of age is associated with subsequent growth and mediates the effect of maternal education on infant growth in urban Zambia.

Mallard SR[1], Houghton LA[2], Filteau S[3], Mullen A[4], Nieuwelink J[3], Chisenga M[5], Siame J[5], Gibson RS[2].

Department of Human Nutrition, University of Otago, Dunedin, New Zealand; Department of Human Nutrition, University of Otago, Dunedin, New Zealand; Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; Diabetes and Nutritional Sciences Division, King's College School of Medicine, London, UK; ; University Teaching Hospital, Lusaka, Zambia.

BACKGROUND:

Although numerous cross-sectional studies have shown an association between WHO infant and young child feeding (IYCF) indicators and child anthropometric measures, limited longitudinal evidence exists linking these indicators with subsequent growth.

OBJECTIVES:

The purpose of this study was to investigate whether meeting WHO IYCF indicators at 6 and 12 mo of age was associated with growth to 18 mo of age and if dietary diversity mediated the relation between household wealth, maternal education, and child growth.

METHODS:

We used longitudinal data on 811 infants in the CIGNIS (Chilenje Infant Growth, Nutrition, Infection Study), a randomized controlled trial comparing the effect of micronutrient-fortified porridges on infant growth in Lusaka, Zambia. Twenty-four-h diet recalls were conducted at 6 and 12 mo of age, and length and weight measurements at ages 6 and 18 mo were used to produce height-for-age Z-scores (HAZs) and weight-for-height Z-scores (WHZs). Information on household assets was used to generate a household wealth index, and level of maternal education was collected.

RESULTS:

In fully adjusted analyses, iron-rich food intake at 6 mo and greater household wealth and maternal education were positively associated with HAZ at 18 mo (all $P \leq 0.016$). Iron-rich food intake at 6 and 12 mo, achieving a "minimum acceptable diet" at 12 mo, and higher maternal education were associated with greater WHZ at 18 mo (all $P \leq 0.044$). Dietary diversity at 6 mo of age was positively associated with both HAZ and WHZ at 18 mo (both $P \leq 0.001$) and mediated 13.4% and 25.9% of the total effect of maternal education on HAZ and WHZ, respectively, at 18 mo.

CONCLUSIONS:

Our findings indicate that IYCF programs should be targeted toward the early period of complementary food introduction and that policies aimed at increasing formal maternal education may benefit child growth through improved feeding practices. This trial was registered at www.controlled-trials.com as ISRCTN37460449.

J Pediatr (Rio J). 2014 Sep-Oct;90(5):464-71. doi: 10.1016/j.jped.2014.02.002. Epub 2014 Mar 20.

Factors associated with low consumption of fruits and vegetables by preschoolers of low socio-economic level.

Valmórbida JL[1], Vitolo MR[2].

Center for Research in Nutrition, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil.; Department of Nutrition, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil.

OBJECTIVE:

To evaluate factors associated with low consumption of fruits and vegetables among preschoolers from families treated at basic health centers in Porto Alegre, RS, Brazil.

METHODS:

This was a cohort study nested in a randomized field trial. Data collection was performed through structured questionnaires to obtain demographic and dietary data, combined with two 24-hour recalls in the age groups 12-16 months and again at 2-3 years of age. Data on the consumption of one daily serving of fruits (80 g) and vegetables (60 g) were evaluated, as well as consumption of non-recommended foods such as candy, chocolate, and soft drinks. Statistical analyses were performed using Poisson regression with robust estimation.

RESULTS:

A total of 388 children aged 2-3 years were evaluated; of these, 58% and 87.4% did not consume one daily serving of fruits and vegetables, respectively. The following factors were negatively associated with fruit consumption: family income higher than four minimum wages, (p=0.024), lower paternal educational level (p=0.03), and lower fruit consumption at 12-16 months (p=0.002). Factors negatively associated with the consumption of vegetables were low paternal educational level (p=0.033) and consumption of high-sugar content beverages at 12-16 months (p=0.014).

CONCLUSION:

This study demonstrated a high prevalence of children who consumed less than one daily serving of fruit and vegetables; early feeding practices, parental education, and family income were associated with this process.

Food Nutr Bull. 2014 Dec;35(4 Suppl):S188-92.

Meat as complementary food for older breastfed infants and toddlers: a randomized, controlled trial in rural China.

Tang M, Sheng XY, Krebs NF, Hambidge KM.

BACKGROUND:

Because of its contribution to dietary diversity and to favorable intakes of micronutrients, including iron and zinc, meat is hypothesized to be a valuable complementary food for the infant and young child. However, the evidence base remains limited.

OBJECTIVE:

To compare the difference in anthropometric measurements of rural Chinese infants and toddlers 6 to 18 months of age who received a daily supplement of meat or cereal for 12 months.

METHODS:

This cluster-randomized, controlled study provided a daily supplement of either meat (n = 514, 20 clusters) or cereal (n = 957, 40 clusters) starting as a first complementary food at 6 months of age. Anthropometric measurements were assessed longitudinally.

RESULTS:

After 12 months of intervention, the meat group (δ13.01 ± 1.9 cm) had greater (p = .01) linear growth than the cereal group (δ12.75 ± 1.8 cm) and a smaller decrease in length-for-age z-score (LAZ) over time (-0.43 ± 0.72 in the meat group vs. -0.54 ± 0.67 in the cereal group), after

adjustment for baseline length, LAZ, maternal education, work status, and maternal height and weight.

CONCLUSIONS:

Linear growth was modestly greater in the meat group than in the cereal group. LAZ was substantially negative at 6 months, and the intervention did not prevent ongoing decline over the course of the study.

Food Nutr Bull. 2014 Dec;35(4 Suppl):S198-204.

High-nutrition biscuits to increase animal protein in diets of HIV-infected Kenyan women and their children: a study in progress.

Ernst J, Ettyang G, Neumann CG.

BACKGROUND:

Preliminary evidence suggests that improved nutrition early in HIV infection may delay progression to AIDS and delay the initiation or improve the effectiveness of antiretroviral drug therapy. There are few studies that evaluate food-based interventions in drug-naïve, HIV-infected women and their children. Meat provides several nutrients identified as important in maintaining immune function and lean body mass.

OBJECTIVE:

To design supplemental meat and soybean biscuits for use in a randomized trial examining the effect of meat in the diet of drug-naïve, HIV-infected rural Kenyan women on changes in weight, lean body mass, morbidity, nutritional status, and activities of daily living of the women and growth and development of their children.

METHODS:

We designed three supplemental biscuits: one with added dried beef another with added soybean flour, and a wheat biscuit to serve as a control biscuit to be used in a randomized feeding intervention in drug-naïve, HIV-infected rural Kenyan women and their children. The nutritional contents of the different types of biscuit were examined and compared.

RESULTS:

The three biscuits were isocaloric. Meat biscuits provided more lysine, vitamin B12, and bioavailable zinc. Soybean biscuits provided more total and absorbable iron; however, higher fiber and phytate contents may inhibit nutrient absorption. Data analysis for clinical outcomes of the trial is ongoing.

CONCLUSIONS:

The "biscuit model" is useful for nutrition supplementation studies because it can be provided in a blinded and randomized fashion, safely and privately in a home under directly observed consumption by a highly stigmatized population. It is well received by adults and children, and the biscuits can be produced locally with available, simple, affordable technology.

J Nutr. 2014 Nov;144(11):1835-42. doi: 10.3945/jn.114.196139. Epub 2014 Sep 17.

Lipid-based nutrient supplements do not affect the risk of malaria or respiratory morbidity in 6- to 18-month-old Malawian children in a randomized controlled trial.

Mangani C[1], Ashorn P[2], Maleta K[3], Phuka J[3], Thakwalakwa C[4], Dewey K[5], Manary M[6], Puumalainen T[7], Cheung YB[8].

College of Medicine, University of Malawi, Blantyre, Malawi; University of Tampere School of Medicine, Tampere, Finland; University of Tampere School of Medicine, Tampere, Finland; Department of Paediatrics, Tampere University Hospital, Finland, Tampere, Finland; College of Medicine, University of Malawi, Blantyre, Malawi; College of Medicine, University of Malawi, Blantyre, Malawi; University of Tampere School of Medicine, Tampere, Finland; University of California, Davis, Davis, CA; Washington University School of Medicine, St. Louis, MO; Ministry for Social Affairs and Health, Helsinki, Finland;Duke-National University of Singapore Graduate Medical School, National University of Singapore, Singapore, Singapore.

BACKGROUND:

There is evidence to support the use of lipid-based nutrient supplements (LNSs) to promote child growth and development in low-income countries, but there is also a concern regarding the safety of using iron-fortified products in malaria-endemic areas.

OBJECTIVE:

The objective of this study was to test the hypothesis that 6- to 18-mo-old rural Malawian children receiving iron-containing (6 mg/d) LNSs would not have excess morbidity compared with infants receiving no supplementation.

METHODS:

A randomized controlled trial allocated 840 children to receive daily supplementation with 54 g/d LNS with milk protein base (milk-LNS), 54 g/d LNS with soy protein base (soy-LNS), 71 g/d corn-soy blend (CSB), or no supplementation from 6 to 18 mo of age. Morbidity was compared using a non-inferiority margin set at 20% excess morbidity in supplemented groups compared with the nonsupplemented group.

RESULTS:

Baseline characteristics were similar across groups. The proportion of days with febrile illness between 6 and 18 mo was 4.9%, and there were no differences between the groups: 4.9% (95% CI: 4.3, 5.5%), 4.5% (95% CI: 3.9, 5.1%), 4.7% (95% CI: 4.1, 5.3%), and 5.5% (95% CI: 4.7-6.3%) in the milk-LNS, soy-LNS, CSB, and control groups, respectively. The proportion of days with respiratory problems and diarrhea between 6 and 18 mo also did not differ between groups. Compared with controls, the incident rate ratio (95% CI) for clinical malaria was 0.80 (0.59, 1.09), 0.77 (0.56, 1.06), and 0.79 (0.58, 1.08) in milk-LNS, soy-LNS, and CSB, respectively, with 95% CIs confirming non-inferiority. The incidence of febrile episodes, diarrhea, respiratory problems or admission to hospital, prevalence of malaria parasitemia throughout the follow-up, and mean change in hemoglobin concentration from baseline were also similar between the groups.

CONCLUSIONS:

Daily supplementation with 54 g of milk-based or soy protein-based LNS or 71 g of CSB did not result in increases in malaria or respiratory morbidity in children in a malaria-endemic

setting. However, we could not conclude whether LNSs did or did not increase diarrheal morbidity. This trial was registered at clinicaltrials.gov as NCT00524446.

Am J Trop Med Hyg. 2014 Oct;91(4):777-85. doi: 10.4269/ajtmh.14-0093. Epub 2014 Aug 18.

Short-term safety and efficacy of calcium montmorillonite clay (UPSN) in children.

Mitchell NJ[1], Kumi J[1], Aleser M[1], Elmore SE[1], Rychlik KA[1], Zychowski KE[1], Romoser AA[1], Phillips TD[1], Ankrah NA[2].

College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas; Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana; Ejura-Sekyedumase District Hospital, Ejura, Ghana.; College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas; Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana; Ejura-Sekyedumase District Hospital, Ejura, Ghana.

Abstract

Recently, an association between childhood growth stunting and aflatoxin (AF) exposure has been identified. In Ghana, homemade nutritional supplements often consist of AF-prone commodities. In this study, children were enrolled in a clinical intervention trial to determine the safety and efficacy of Uniform Particle Size NovaSil (UPSN), a refined calcium montmorillonite known to be safe in adults. Participants ingested 0.75 or 1.5 g UPSN or 1.5 g calcium carbonate placebo per day for 14 days. Hematological and serum biochemistry parameters in the UPSN groups were not significantly different from the placebo-controlled group. Importantly, there were no adverse events attributable to UPSN treatment. A significant reduction in urinary metabolite (AFM1) was observed in the high-dose group compared with placebo. Results indicate that UPSN is safe for children at doses up to 1.5 g/day for a period of 2 weeks and can reduce exposure to AFs, resulting in increased quality and efficacy of contaminated foods.

Am J Clin Nutr. 2015 Mar;101(3):455-61. doi: 10.3945/ajcn.114.087775. Epub 2014 Dec 24.

Effectiveness in improving knowledge, practices, and intakes of "key problem nutrients" of a complementary feeding intervention developed by using linear programming: experience in Lombok, Indonesia.

Fahmida U[1], Kolopaking R[1], Santika O[1], Sriani S[1], Umar J[1], Htet MK[1], Ferguson E[1].

From the Southeast Asian Ministers of Education Organization Regional Center for Food and Nutrition, Universitas Indonesia, Jakarta, Indonesia (UF, OS, and SS); the Faculty of Psychology, Universitas Islam Negeri Syarif Hidayatullah, Jakarta, Indonesia (RK and JU); the Center of Community Health and Population Studies, The Research Institute, Trisakti University, Jakarta, Indonesia (MKH); and the London School of Hygiene and Tropical Medicine, London, United Kingdom (EF).

BACKGROUND:

Complementary feeding recommendations (CFRs) with the use of locally available foods can be developed by using linear programming (LP). Although its potential has been shown for planning phases of food-based interventions, the effectiveness in the community setting has not been tested to our knowledge.

OBJECTIVE:

We aimed to assess effectiveness of promoting optimized CFRs for improving maternal knowledge, feeding practices, and child intakes of key problem nutrients (calcium, iron, niacin, and zinc).

DESIGN:

A community-intervention trial with a quasi-experimental design was conducted in East Lombok, West Nusa Tenggara Province, Indonesia, on children aged 9-16 mo at baseline. A CFR group (n = 240) was compared with a non-CFR group (n = 215). The CFRs, which were developed using LP, were promoted in an intervention that included monthly cooking sessions and weekly home visits. The mother's nutrition knowledge and her child's feeding practices and the child's nutrient intakes were measured before and after the 6-mo intervention by using a structured interview, 24-h recall, and 1-wk food-frequency questionnaire.

RESULTS:

The CFR intervention improved mothers' knowledge and children's feeding practices and improved children's intakes of calcium, iron, and zinc. At the end line, median (IQR) nutrient densities were significantly higher in the CFR group than in the non-CFR group for iron [i.e., 0.6 mg/100 kcal (0.4-0.8 mg/100 kcal) compared with 0.5 mg/100 kcal (0.4-0.7 mg/100 kcal)] and niacin [i.e., 0.8 mg/100 kcal (0.5-1.0 mg/100 kcal) compared with 0.6 mg/100 kcal (0.4-0.8 mg/100 kcal)]. However, median nutrient densities for calcium, iron, niacin, and zinc in the CFR group (23, 0.6, 0.7, and 0.5 mg/100 kcal, respectively) were still below desired densities (63, 1.0, 0.9, and 0.6 mg/100 kcal, respectively).

CONCLUSIONS:

The CFRs significantly increased intakes of calcium, iron, niacin, and zinc, but nutrient densities were still below desired nutrient densities. When the adoption of optimized CFRs is constrained by economic access for or acceptability of nutrient-dense foods, other strategies need to be incorporated into interventions to ensure adequate intakes of these nutrients.

Breastfeeding

J Nutr. 2014 Jul;144(7):1120-4. doi: 10.3945/jn.113.190124. Epub 2014 May 8.

Integrating group counseling, cell phone messaging, and participant-generated songs and dramas into a microcredit program increases Nigerian women's adherence to international breastfeeding recommendations.

Flax VL[1], Negerie M[2], Ibrahim AU[2], Leatherman S[3], Daza EJ[4], Bentley ME[5].

Carolina Population Center and Departments of Nutrition,; Partners for Development, Abuja, Nigeria.; Health Policy and Management,; Carolina Population Center and Departments of Biostatistics, University of North Carolina, Chapel Hill, NC; Carolina Population Center and Departments of Nutrition.

Abstract

In northern Nigeria, interventions are urgently needed to narrow the large gap between international breastfeeding recommendations and actual breastfeeding practices. Studies of integrated microcredit and community health interventions documented success in modifying health behaviors but typically had uncontrolled designs. We conducted a cluster-randomized controlled trial in Bauchi State, Nigeria, with the aim of increasing early breastfeeding initiation and exclusive breastfeeding among female microcredit clients. The intervention had 3 components. Trained credit officers led monthly breastfeeding learning sessions during regularly scheduled microcredit meetings for 10 mo. Text and voice messages were sent out weekly to a cell phone provided to small groups of microcredit clients (5-7 women). The small groups prepared songs or dramas about the messages and presented them at the monthly microcredit meetings. The control arm continued with the regular microcredit program. Randomization occurred at the level of the monthly meeting groups. Pregnant clients were recruited at baseline and interviewed again when their infants were aged ≥6 mo. Logistic regression models accounting for clustering were used to estimate the odds of performing recommended behaviors. Among the clients who completed the final survey (n = 390), the odds of exclusive breastfeeding to 6 mo (OR: 2.4; 95% CI: 1.4, 4.0) and timely breastfeeding initiation (OR: 2.6; 95% CI: 1.6, 4.1) were increased in the intervention vs. control arm. Delayed introduction of water explained most of the increase in exclusive breastfeeding among clients receiving the intervention. In conclusion, a breastfeeding promotion intervention integrated into microcredit increased the likelihood that women adopted recommended breastfeeding practices. This intervention could be scaled up in Nigeria, where local organizations provide microcredit to >500,000 clients. Furthermore, the intervention could be adopted more widely given that >150 million women, many of childbearing age, are involved in microfinance globally.

Community nutrition and agriculture

Food Nutr Bull. 2014 Sep;35(3):312-26.

Community development and livestock promotion in rural Nepal: effects on child growth and health.

Miller LC, Joshi N, Lohani M, Rogers B, Loraditch M, Houser R, Singh P, Mahato S.

BACKGROUND:

More than 50% of children in Nepal are malnourished. Economic growth and poverty reduction are not always sufficient to improve the health and nutritional status of children. Heifer Nepal uses livestock training as a tool for community development and poverty alleviation but does not directly address child health and nutrition.

OBJECTIVE:

To systematically assess the effects of Heifer activities on child health and nutrition.

METHODS:

The study was a 2-year, longitudinal, randomized, controlled trial in six communities in Nepal (both Terai and hills), pair-matched for specific characteristics, randomly assigned to receive Heifer community development activities at baseline (intervention) or 1 year (control). At 6-month intervals over a period of 2 years, child anthropometric and comprehensive household surveys were performed.

RESULTS:

Four hundred fifteen households were enrolled containing 607 children 6 months to 5 years of age. The intervention and control communities were equivalent for baseline socioeconomic status, household size, ownership of land and animals, and child nutrition and health. At 12 months (prior to animal donations), the Terai intervention group had improved child weight ($p = .04$), improved child height ($p = .05$), and reduced sick days ($p = .03$), as well as increased household income ($p = .004$), increased ownership of animals ($p = .04$) and land ($p = .04$), and improved sanitation practices ($p < .01$). In all districts, longer participation in Heifer activities corresponded to more improvement in child height-for-age z-scores.

CONCLUSIONS:

Heifer interventions resulted in improved socioeconomic status and household income per family member. Children under 60 months of age in the intervention group had greater incremental improvement in height-for-age and weight-for-age z-scores than children in the control group, and longer participation in Heifer activities was associated with better growth. Poverty alleviation programs, such as Heifer, may indirectly benefit child growth.

J Nutr. 2015 Jun;145(6):1317-24. doi: 10.3945/jn.114.203539. Epub 2015 Apr 22.

A 2-year integrated agriculture and nutrition and health behavior change communication program targeted to women in burkina faso reduces anemia, wasting, and diarrhea in children 3-12.9 months of age at baseline: a cluster-randomized controlled trial.

Olney DK[1], Pedehombga A[2], Ruel MT[3], Dillon A[4].

Poverty Health and Nutrition Division, International Food Policy Research Institute, Washington, DC; Helen Keller International, Ouagadougou, Burkina Faso; Poverty Health and Nutrition Division, International Food Policy Research Institute, Washington, DC; Department of Agricultural, Food, and Resource Economics, Michigan State University, East Lansing, MI.

BACKGROUND:

Among young children in Burkina Faso, anemia and chronic and acute undernutrition are widespread.

OBJECTIVE:

This study assessed the impact of Helen Keller International's (HKI) 2-y integrated agriculture [homestead food production (HFP)] and nutrition and health behavior change communication (BCC) program, targeted to women, on children's (3-12.9 mo old at baseline) anthropometry (stunting, wasting, and underweight), mean hemoglobin (Hb), anemia (Hb < 11 g/dL), and diarrhea prevalence.

METHODS:

We used a cluster-randomized controlled trial, with 55 villages randomly assigned to a control group (n = 25) or 1 of 2 treatment groups (n = 15 each), which differed by who delivered the BCC messages [older women leaders or health committee (HC) members]. We used difference-in-difference (DID) estimates to assess impacts on child outcomes.

RESULTS:

We found marginally significant (P < 0.10) impacts on Hb (DID: 0.51 g/dL; P = 0.07) and wasting [DID: -8.8 percentage point (pp); P = 0.08] and statistically significant (P < 0.05) impacts on diarrhea (-15.9 pp; P = 0.00) in HC compared with control villages among children aged 3-12.9 mo and larger impacts for anemia (DID: -14.6 pp; P = 0.03) and mean Hb (DID: 0.74 g/dL; P = 0.03) among younger children (aged 3-5.9 mo). However, we found no significant impacts on stunting or underweight prevalence. Plausibility was supported by greater improvements in women's agricultural production and maternal infant and young child feeding and care knowledge and practices in HC compared with control villages.

CONCLUSIONS:

HKI's 2-y integrated HFP+BCC program (HC group) significantly improved several child outcomes, including wasting (marginal), diarrhea, Hb, and anemia, especially among the youngest children. This is the first cluster-randomized controlled trial of an HFP program that documents statistically significant positive effects on these child nutrition outcomes. This trial was registered at clinicaltrials.gov as NCT01825226.

Obesity

Zhonghua Liu Xing Bing Xue Za Zhi. 2014 Jul;35(7):773-8.

[Evaluation on the effectiveness of intervention comprehensive program on child obesity, using Generalized Estimating Equation].

[Article in Chinese]

Cao Z[1], Wang S[2], Zheng W[1], Guo J[1], Qu S[1].

Key Laboratory of Public Health Safety, Ministry of Education-Department of Maternal and Children and Adolescent Health, School of Public Health, Fudan University, Shanghai, China.

OBJECTIVE:

To evaluate the effect of child obesity intervention comprehensive program on the improvement of overweight, obese control and knowledge-attitude-practice.

METHODS:

The study design was under cluster-randomized controlled trial, with 965 children in the intervention and 895 children in the control groups. Repeated measurement data on child obesity was analyzed through Generalized Estimating Equation models.

RESULTS:

The risk of becoming overweight or obesity in the intervention group was 0.824 times more than children in the control group, showing a reduction of 17.6% the risk of being overweight or obese (P = 0.031). In addition, the possibility of increasing one unit of correct rate on obesity

related knowledge, children in the intervention group children was 1.044 times (P = 0.001)than in the control group. On the mean obesity related correct attitude rate, it was 1.023 times (P = 0.001) in the intervention group of the control group. Regarding the possibility of increasing one unit om the mean obesity related behavior score, children in the intervention group was 1.522 times (P = 0.001)than those in the control group (P = 0.046).

CONCLUSION:

The comprehensive child obesity intervention program could effectively reduce the risk of developing overweight or obesity and improving the obesity related knowledge, attitude and behavior in children.

J Telemed Telecare. 2015 May 29. pii: 1357633X15586642. [Epub ahead of print]

Treating rural paediatric obesity through telemedicine vs. telephone: Outcomes from a cluster randomized controlled trial.

Davis AM[1], Sampilo M[2], Gallagher KS[3], Dean K[4], Saroja MB[5], Yu Q[6], He J[6], Sporn N[7].

University of Kansas Medical Center, Department of Pediatrics, USA Center for Children's Healthy Lifestyles & Nutrition, USA; Center for Children's Healthy Lifestyles & Nutrition, USA University of Kansas, Department of Clinical Child Psychology, USA.; Boston Children's Hospital, Harvard Medical School, Department of Psychiatry, USA.; University of Kansas Medical Center, Department of Pediatrics, USA.; Christian Medical College, Vellore, India.; University of Kansas Medical Center, Department of Biostatistics, USA.; University of Kansas, Department of Psychology, USA.

OBJECTIVE:

The objective of the current study was to examine the feasibility of telemedicine vs. telephone for the delivery of a multidisciplinary weekly family-based behavioural group intervention to treat paediatric obesity delivered to families living in rural areas using a randomized controlled trial methodology.

METHODS:

103 rural children and their families were recruited. Feasibility measures included participant satisfaction, session attendance and retention. Treatment outcome measures included child Body Mass Index z-score (BMIz), parent BMI, 24-hour dietary recalls, accelerometer data, the child behavior checklist and the behavioral pediatrics feeding assessment scale.

RESULTS:

Participants were highly satisfied with the intervention both via telemedicine and via telephone. Completion rates were much higher than for other paediatric obesity intervention programmes, and both methodologies were highly feasible. There were no differences in telemedicine and telephone groups on primary outcomes.

CONCLUSION:

Both telemedicine and telephone intervention appear to be feasible and acceptable methods of delivering paediatric obesity treatment to rural children.

Oncology

(see also HIV – management of HIV related conditions)

Support Care Cancer. 2015 Apr 8. [Epub ahead of print]

Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: a randomized, double-blind, placebo-controlled trial.

Bakhshi S[1], Batra A, Biswas B, Dhawan D, Paul R, Sreenivas V.

Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India,

BACKGROUND:

Aprepitant, a neurokinin-1 receptor antagonist, in combination with 5 HT-3 antagonist and dexamethasone is recommended in adults receiving moderately and highly emetogenic chemotherapy to reduce chemotherapy-induced vomiting (CIV). Data for use of aprepitant in children is limited and hence aprepitant is not recommended by Pediatric Oncology Group of Ontario guidelines for prevention of CIV in children <12 years.

METHODS:

A randomized, double-blind, placebo-controlled trial was conducted at a single center in chemotherapy naïve children (5-18 years) receiving highly emetogenic chemotherapy. All patients received intravenous ondansetron (0.15 mg/kg) and dexamethasone (0.15 mg/kg) prior to chemotherapy followed by oral ondansetron and dexamethasone. Patients randomly assigned to aprepitant arm received oral aprepitant (15-40 kg = days 1-3, 80 mg; 41-65 kg = day 1, 125 mg and days 2-3, 80 mg) 1 h before chemotherapy. Control group received placebo as add-on therapy. Primary outcome measure was the incidence of acute moderate to severe vomiting, which was defined as more than two vomiting episodes within 24 h after the administration of the first chemotherapy dose until 24 h after the last chemotherapy dose in the block. Complete response (CR) was defined as absence of vomiting and retching during the specified phase.

RESULTS:

Of the 96 randomized patients, three were excluded from analysis; 93 patients were analyzed (50 in aprepitant arm and 43 in placebo arm). Acute moderate and severe vomiting was reported in 72 % patients receiving placebo and 38 % patients receiving aprepitant ($p = 0.001$). Complete response rates during acute phase were significantly higher in aprepitant arm (48 vs. 12 %, $p < 0.001$). No major adverse effects were reported by patients/guardians.

CONCLUSIONS:

This double-blind, randomized, placebo-controlled trial shows that aprepitant significantly decreases the incidence of CIV during acute phase when used as an add-on drug with ondansetron and dexamethasone in children receiving highly emetogenic chemotherapy.

Ophthalmology

BMJ. 2014 Sep 23;349:g5740. doi: 10.1136/bmj.g5740.

Effect of providing free glasses on children's educational outcomes in China: cluster randomized controlled trial.

Ma X[1], Zhou Z[2], Yi H[3], Pang X[4], Shi Y[5], Chen Q[6], Meltzer ME[6], le Cessie S[7], He M[6], Rozelle S[8], Liu Y[6], Congdon N[9].

Department of Agriculture and Resource Economics, University of California, Davis, Davis, CA, USA Stanford Center For International Development, Stanford University, Stanford, CA, USA; Key Laboratory of Ophthalmology and Division of Preventive Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China; Center for Chinese Agricultural Policy, Institute of Geographical Sciences and Natural Resources Research, Chinese Academy of Sciences, Beijing, China.; School of Agricultural Economics and Rural Development, Renmin University of China, Beijing, China.; School of Economic Management, Xibei University, Xi'an, China.; Key Laboratory of Ophthalmology and Division of Preventive Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China.; Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, Netherlands.; Freeman Spogli Institute of International Studies, Stanford University, Stanford, CA, USA.; Key Laboratory of Ophthalmology and Division of Preventive Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China ORBIS International, New York, NY, USA ncongdon1@gmail.com.

OBJECTIVE:

To assess the effect of provision of free glasses on academic performance in rural Chinese children with myopia.

DESIGN:

Cluster randomized, investigator masked, controlled trial.

SETTING:

252 primary schools in two prefectures in western China, 2012-13.

PARTICIPANTS:

3177 of 19,934 children in fourth and fifth grades (mean age 10.5 years) with visual acuity <6/12 in either eye without glasses correctable to >6/12 with glasses. 3052 (96.0%) completed the study.

INTERVENTIONS:

Children were randomized by school (84 schools per arm) to one of three interventions at the beginning of the school year: prescription for glasses only (control group), vouchers for free glasses at a local facility, or free glasses provided in class.

MAIN OUTCOME MEASURES:

Spectacle wear at endline examination and end of year score on a specially designed mathematics test, adjusted for baseline score and expressed in standard deviations.

RESULTS:

Among 3177 eligible children, 1036 (32.6%) were randomized to control, 988 (31.1%) to vouchers, and 1153 (36.3%) to free glasses in class. All eligible children would benefit from glasses, but only 15% wore them at baseline. At closeout glasses wear was 41% (observed) and

68% (self reported) in the free glasses group, and 26% (observed) and 37% (self reported) in the controls. Effect on test score was 0.11 SD (95% confidence interval 0.01 to 0.21) when the free glasses group was compared with the control group. The adjusted effect of providing free glasses (0.10, 0.002 to 0.19) was greater than parental education (0.03, -0.04 to 0.09) or family wealth (0.01, -0.06 to 0.08). This difference between groups was significant, but was smaller than the prespecified 0.20 SD difference that the study was powered to detect.

CONCLUSIONS:

The provision of free glasses to Chinese children with myopia improves children's performance on mathematics testing to a statistically significant degree, despite imperfect compliance, although the observed difference between groups was smaller than the study was originally designed to detect. Myopia is common and rarely corrected in this setting.Trial Registration Current Controlled Trials ISRCTN03252665.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4172821/pdf/bmj.g5740.pdf

Acta Ophthalmol. 2014 Aug;92(5):e358-61. doi: 10.1111/aos.12375. Epub 2014 Apr 14.

Outcome of paediatric cataract surgery with primary posterior capsulotomy and anterior vitrectomy using intra-operative preservative-free triamcinolone acetonide.

Gupta R[1], Ram J, Sukhija J, Singh R.
Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

PURPOSE:

To evaluate the intra-operative and postoperative outcome of paediatric cataract surgery with primary posterior capsulotomy (PPC) and anterior vitrectomy using intra-operative preservative-free triamcinolone acetonide.

METHODS:

In this prospective, interventional case-control study, 20 Children who underwent cataract surgery for both eyes were enrolled and their eyes were randomized into two groups. Group A consists of 20 eyes in which standard phacoaspiration with PPC with intracameral triamcinolone was used, and Group B consists of 20 eyes in which triamcinolone were not used. Intra-operative complications and postoperative outcome like intraocular pressure (IOP), posterior synechiae, pigment deposits and posterior capsule opacification (PCO) were studied.

RESULTS:

In both groups, age range varied between 2-8 years comprising 18 males and two females. The mean postoperative IOP did not show any significant variation during 6-month follow-up. In study group, all the 20 eyes were quiet at 2 weeks, while there was cellular reaction 1+ in four eyes (20%) and nil in 16 eyes (80%) at 2 week in the control group ($p = 0.035$). Pigment deposits on IOL optic was seen in two eyes (10%) of the study group while in control group, IOL deposits were present in 14 eyes (70%) ($p = 0.001$). Posterior capsule opacification was seen in two eyes (10%) in control group at 3 months while none occurred in study group.

CONCLUSIONS:

Intra-operative use of preservative-free triamcinolone acetonide led to less anterior chamber inflammation and pigment deposits on IOL optic postoperatively compared to those eyes where it was not used.

Eur J Ophthalmol. 2014 Sep-Oct;24(5):643-9. doi: 10.5301/ejo.5000438. Epub 2014 Feb 13.

Sub-Tenon block does not provide superior postoperative analgesia vs intravenous fentanyl in pediatric squint surgery.

Ramachandran R[1], Rewari V, Chandralekha C, Sinha R, Trikha A, Sharma P.

Department of Anaesthesiology, All India Institute of Medical Sciences, Delhi - India.

PURPOSE:

We evaluated the efficacy of sub-Tenon block in decreasing perioperative pain, incidence of intraoperative oculocardiac reflex (OCR), and postoperative nausea and vomiting (PONV) in pediatric squint surgery.

METHODS:

A total of 67 children age 2-12 years, American Society of Anesthesiologists Physical Status 1 and 2, were randomized to receive either sub-Tenon block (ST) in the operative eye or 2 mcg/kg of intravenous fentanyl (F) for squint surgery after induction of general anesthesia in this double-blind study. Postoperative pain was measured by either modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) or Visual Analogue Scale (VAS). Pain in the postoperative period (up to 2 hours) was measured as the primary endpoint. Other parameters measured in the groups were intraoperative hemodynamics, postoperative modified CHEOPS or VAS at shifting, 1, 2, 6, 12, and 24 hours after surgery, incidence of intraoperative OCR, and PONV at shifting, 30 minutes, 1, 2, 6, 12, and 24 hours after surgery.

RESULTS:

There was no statistical difference in the postoperative pain scores in the recovery room up to 2 hours after surgery. The VAS and CHEOPS scores were not different in the groups up to 24 hours after surgery. The incidence of OCR was significantly higher in group F than group ST. The incidence of PONV was significantly higher in group F than group ST at 30 minutes and 1 hour after the surgery (41%, 47% vs 19%, 9%, respectively, $p<0.05$). However, there was no statistically significant difference in intraoperative hemodynamics and PONV scores after 2 hours in the postanesthesia care unit.

CONCLUSIONS:

Use of sub-Tenon block does not decrease the incidence of postoperative pain significantly in children undergoing squint surgery. However, it leads to a statistically significant decrease in the incidence of intraoperative OCR and PONV in the early recovery period in these patients.

http://www.eur-j-ophthalmol.com/article/sub-tenon-block-does-not-provide-superior-postoperative-analgesia-vs-intravenous-fentanyl-in-pediatric-squint-surgery

Trachoma

(See also Hygiene)

Oral health / dentistry

J Clin Diagn Res. 2015 Feb;9(2):ZC06-9. doi: 10.7860/JCDR/2015/10942.5532. Epub 2015 Feb 1.

Effect of Probiotic Containing Ice-cream on Salivary Mutans Streptococci (SMS) Levels in Children of 6-12 Years of Age: A Randomized Controlled Double Blind Study with Six-months Follow Up.

Ashwin D[1], Ke V[2], Taranath M[3], Ramagoni NK[4], Nara A[5], Sarpangala M[6].

Senior Lecturer, Department of Pediatric and Preventive Dentistry, Kannur Dental College , Anjarakandy, Kannur, Kerala, India ; Professor & Head, Department of Pediatric and Preventive Dentistry, Navodaya Dental College , Raichur, Karnataka, India .; Professor, Department of Pediatric and Preventive Dentistry, Navodaya Dental College , Raichur, Karnataka State, India ; Reader, Department of Pediatric and Preventive Dentistry, Navodaya Dental College , Raichur, Karnataka State, India ; Reader, PMNM Dental College & Hospital , Bagalkot, Karnataka, India; Senior Lecturer, Department Periodontics, Kannur Dental College , Anjarakandy, Kannur, Kerala, India.

INTRODUCTION:

To evaluate the caries risk based on the salivary levels of streptococcus mutans in children of 6-12 years of age group before and after consuming probiotic ice-cream containing Bifidobacterium lactis Bb-12 and Lactobacillus acidophilus La-5.

MATERIALS AND METHODS:

A double blind, placebo controlled trial was carried out in 60 children aged between 6 to 12 years with zero decayed, missing, and filled teeth (DMFT). They were randomly divided into two equal groups. Saliva sample were collected before the consumption of ice-cream and Streptococcus mutans count was calculated and recorded as baseline data. For the next seven days both the groups were given ice creams marked as A and B. Saliva samples were collected after ice-cream consumption at the end of study period and also after a washout period of 30 days and again after six months. Samples were inoculated and colonies were counted.

RESULTS:

On statistical evaluation by students paired t-test, probiotic ice-cream brought significant reduction in the Streptococcus mutans count after seven days of ice-cream ingestion ($p<0.001$) and also after 30 d of washout period ($p<0.001$). There was no significant reduction ($p=0.076$) by normal ice-cream consumption. After six months of the study period in both the groups the salivary levels of Streptococcus mutans was similar to the baseline.

CONCLUSION:

Probiotic ice-cream containing Bifidobacterium lactis Bb-12 and Lactobacillus acidophilus La-5 can cause reduction in caries causative organism. The dosage of the probiotic organisms for the long term or synergetic effect on the oral health are still needed to be explored.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4378797/pdf/jcdr-9-ZC06.pdf

Phytomedicine. 2014 Jul-Aug;21(8-9):1043-7. doi: 10.1016/j.phymed.2014.04.021. Epub 2014 May 23.

The efficacy of three formulations of Lippia sidoides Cham. essential oil in the reduction of salivary Streptococcus mutans in children with caries: a randomized, double-blind, controlled study.

Lobo PL[1], Fonteles CS[2], Marques LA[3], Jamacaru FV[3], Fonseca SG[4], de Carvalho CB[5], de Moraes ME[3].

Department of Clinical Dentistry, School of Dentistry-Campus Sobral, Federal University of Ceará, Brazil.; Postgraduate Program in Dentistry, Department of Clinical Dentistry, School of Dentistry, Federal University of Ceará, Brazil.; Clinical Pharmacology Unit, Department of Pharmacology, School of Medicine, Federal University of Ceará, Brazil.; Laboratory of Pharmaceutical Science, School of Pharmacy, Federal University of Ceará, Brazil.; Department of Pathology and Legal Medicine, School of Medicine, Federal University of Ceará, Brazil.

Abstract

Essential oils of many plants have been previously tested in the treatment of oral diseases and other infections. This study was a randomized, double-blind, in parallel with an active control study, which aimed to evaluate the efficacy of three formulations of the Lippia sidoides Cham. essential oil (LSO) in the reduction of salivary Streptococcus mutans in children with caries. 81 volunteers, aged 6-12 years, both genders, with caries, were recruited to participate in this study, and randomly assigned to either one of five different groups. Each group received topical treatment with either 1.4% LSO toothpaste, 1.4% LSO gel, 0.8% LSO mouthwash, 1% chlorhexidine gel, or 0.12% chlorhexidine mouthwash. A 5-ml volume of each gel was placed inside disposable trays, and applied for 1 min, every 24h, for 5 consecutive days. The mouthwash groups used 5-ml volume of a mouthwash inside disposable syringes. In the toothpaste group, children brushed their teeth for 1 min, once a day for 5 days. Saliva was collected before and after treatment. MS colonies were counted, isolated and confirmed through biochemical tests. Differences in MS levels measured in different days within the same treatment group was only verified with LSO toothpaste, chlorhexidine gel and chlorhexidine mouthwash. Comparison between groups of LSO mouthwash, toothpaste and gel showed that the toothpaste group expressed significantly lower MS levels than the mouthwash and gel groups at day-30. Chlorhexidine significantly reduced MS levels after 5 days of treatment, but these levels returned to baseline in other periods of the study. LSO toothpaste reduced MS levels after 5 days of treatment, and MS levels remained low and did not return to baseline during subsequent analysis. Hence, LSO toothpaste demonstrated the most long-lasting MS reduction in saliva, whereas other LSO formulations did not effectively reduce MS levels in children with dental caries.

Poisoning and toxins

Saudi J Anaesth. 2015 Jan;9(1):49-54. doi: 10.4103/1658-354X.146306.

Is the World Health Organization-recommended dose of pralidoxime effective in the treatment of organophosphorus poisoning? A randomized, double-blinded and placebo-controlled trial.

Syed S[1], Gurcoo SA[1], Farooqui AK[1], Nisa W[1], Sofi K[1], Wani TM[2].

Department of Anesthesiology and Critical Care, Sheri Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir, India.; Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA.

BACKGROUND:

Organophosphorus poisoning (OPP) is a major global public health problem. Pralidoxime has been used in a complimentary role to atropine for the management of OPP. World Health Organization (WHO) recommends use of pralidoxime but studies regarding its role have been inconclusive, ranging from being ineffective to harmful or beneficial.

MATERIALS AND METHODS:

The present study was undertaken to evaluate the effectiveness of pralidoxime. Eddleston's study was the most compelling factor for our study, as he showed worst outcomes using pralidoxime. Our practice of continuous use of pralidoxime was based on the WHO guidelines and the study by Pawar (2006), which showed better outcome with higher doses of pralidoxime. These conflicting results suggested that a re-evaluation of its use in our clinical practice was indicated.

RESULTS:

There was no difference in mortality rates, hemodynamic parameters and atropine requirements between the AP and A groups. Mean duration of ventilation (3.6 ± 4.6 in AP group vs. 3.6 ± 4.4 in A group) and Intensive Care Unit stay (7.1 ± 5.4 in AP group vs. 6.8 ± 4.7 in A group) was comparable. Serum sodium concentrations showed a correlation with mortality, with lower concentrations associated with better outcomes.

CONCLUSION:

The study suggests that add-on WHO-recommended pralidoxime therapy does not provide any benefit over atropine monotherapy. Adding pralidoxime does not seem to be beneficial and at the same time does not result in increased mortality rates. Our practice changed after completion of this study, and it has proven to be of significant benefit to patients who had to bear the expense of treatment.

KEYWORDS:

Acetyl-cholinesterase; atropine; organophosphorous poisoning; pralidoxime; pseudo-cholinesterase; ventilation

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4279350/

MBio. 2014 Oct 7;5(5):e01580-14. doi: 10.1128/mBio.01580-14.

Randomized open-label pilot study of the influence of probiotics and the gut microbiome on toxic metal levels in Tanzanian pregnant women and school children.

Bisanz JE, Enos MK, Mwanga JR[1], Changalucha J[1], Burton JP, Gloor GB[2], Reid G[3].

National Institute for Medical Research, Mwanza, Tanzania. Department of Biochemistry, The University of Western Ontario, London, Canada.

Abstract

Exposure to environmental toxins is a 21st century global health problem that is often the result of dietary intake. Although efforts are made to reduce dietary toxin levels, they are often unsuccessful, warranting research into novel methods to reduce host exposure. Food-grade microbes that can be delivered to the gastrointestinal tract and that are capable of sequestering toxins present a safe and cost-effective intervention. We sought to investigate the potential for probiotic-supplemented yogurt to lower heavy metal levels in at-risk populations of pregnant women and in children in Mwanza, Tanzania, and to examine the microbiome in relation to toxin levels. Two populations suspected to have high toxic metal exposures were studied. A group of 44 school-aged children was followed over 25 days, and 60 pregnant women were followed over their last two trimesters until birth. A yogurt containing 10(10) CFU Lactobacillus rhamnosus GR-1 per 250 g was administered, while control groups received either whole milk or no intervention. Changes in blood metal levels were assessed, and the gut microbiomes of the children were profiled by analyzing 16S rRNA sequencing via the Ion Torrent platform. The children and pregnant women in the study were found to have elevated blood levels of lead and mercury compared to age- and sex-matched Canadians. Consumption of probiotic yogurt had a protective effect against further increases in mercury (3.2 nmol/liter; P = 0.035) and arsenic (2.3 nmol/liter; P = 0.011) blood levels in the pregnant women, but this trend was not statistically significant in the children. Elevated blood lead was associated with increases in Succinivibrionaceae and Gammaproteobacteria relative abundance levels in stool. Importance: Probiotic food produced locally represents a nutritious and affordable means for people in some developing countries to counter exposures to toxic metals. Further research and field trials are warranted to explore this approach in countries where communities are located near mining sites and agricultural areas, two types of areas where toxins are likely to be elevated.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4196227/pdf/mBio.01580-14.pdf

Quality of care

BMC Health Serv Res. 2014 Jul 18;14:312. doi: 10.1186/1472-6963-14-312.

Assessment of paediatric inpatient care during a multifaceted quality improvement intervention in Kenyan district hospitals--use of prospectively collected case record data.

Mwaniki P[1], Ayieko P, Todd J, English M.

KEMRI/Wellcome Trust Research Programme, Nairobi, Kenya.

BACKGROUND:

In assessing quality of care in developing countries, retrospectively collected data are usually used given their availability. Retrospective data however suffer from such biases as recall bias

and non-response bias. Comparing results obtained using prospectively and retrospectively collected data will help validate the use of the easily available retrospective data in assessing quality of care in past and future studies.

METHODS:

Prospective and retrospective datasets were obtained from a cluster randomized trial of a multifaceted intervention aimed at improving paediatric inpatient care conducted in eight rural Kenyan district hospitals by improving management of children admitted with pneumonia, malaria and diarrhea and/or dehydration. Four hospitals received a full intervention and four a partial intervention. Data were collected through 3 two weeks surveys conducted at baseline, after 6 and 18 months. Retrospective data was sampled from paediatric medical records of patients discharged in the preceding six months of the survey while prospective data was collected from patients discharged during the two week period of each survey. Risk Differences during post-intervention period of 16 quality of care indicators were analyzed separately for prospective and retrospective datasets and later plotted side by side for comparison.

RESULTS:

For the prospective data there was strong evidence of an intervention effect for 8 of the indicators and weaker evidence of an effect for one indicator, with magnitude of effect sizes varying from 23% to 60% difference. For the retrospective data, 10 process (these include the 8 indicators found to be statistically significant in prospective data analysis) indicators had statistically significant differences with magnitude of effects varying from 10% to 42%. The bar-graph comparing results from the prospective and retrospective datasets showed similarity in terms of magnitude of effects and statistical significance for all except two indicators.

CONCLUSION:

Multifaceted interventions can help improve adoption of clinical guidelines and hence improve the quality of care. The similar inference reached after analyses based on prospective assessment of case management is a useful finding as it supports the utility of work based on examination of retrospectively assembled case records allowing longer time periods to be studied while constraining costs.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110369/pdf/1472-6963-14-312.pdf

Research methods

BMC Res Notes. 2014 Oct 9;7:706. doi: 10.1186/1756-0500-7-706.

Lessons in participant retention in the course of a randomized controlled clinical trial.

Idoko OT[1], Owolabi OA, Odutola AA, Ogundare O, Worwui A, Saidu Y, Smith-Sanneh A, Tunkara A, Sey G, Sanyang A, Mendy P, Ota MO.

Medical Research Council Unit, Banjul, The Gambia.

BACKGROUND:

Clinical trials are increasingly being conducted as new products seek to enter the market. Deployment of such interventions is based on evidence obtained mainly from the gold standard

of randomized controlled clinical trials (RCCT). A crucial factor in the ability of RCCTs to provide credible and generalisable data is sample size and retention of the required number of subjects at completion of the follow-up period. However, recruitment and retention in clinical trials are hindered by prevalent peculiar challenges in Africa that need to be circumvented. This article shares experiences from a phase II trial that recorded a high retention rate at 14 months follow-up at a new clinical trial site.

METHODS:

Mothers bringing children less than two months of age to the health facility were given information and invited to have their child enrolled if the inclusion criteria were fulfilled. Participants were enrolled over 8 months. Trial procedures, duration and risks/benefits were painstakingly and sequentially explained to the communities, parents and relevant relatives before and during the trial period. The proportions of participants that completed or did not complete the trial were analyzed including the reasons for failure to complete all trial procedures.

RESULTS:

1044 individuals received information regarding the trial of which 371 returned for screening. 300 (81%) of them who fulfilled the inclusion criteria and did not meet any exclusion criteria were enrolled and 94% of these completed the trial. Consent withdrawal was the main reason for not completing the trial largely (75%) due to the father not being involved at the point of consenting or parents no longer being comfortable with blood sampling.

CONCLUSIONS:

Participant retention in clinical trials remains a crucial factor in ensuring generalisability of trial data. Appropriate measures to enhance retention should include continuous community involvement in the process, adequate explanation of trial procedures and risks/benefits; and innovative tracing of participants adapted for the setting.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4200120/pdf/13104_2014_Article_3235.pdf

J Am Med Inform Assoc. 2015 Jan;22(1):51-64. doi: 10.1136/amiajnl-2014-002845. Epub 2014 Oct 20.

Increasing the response rate of text messaging data collection: a delayed randomized controlled trial.

Li Y[1], Wang W[1], Wu Q[1], van Velthoven MH[2], Chen L[1], Du X[1], Zhang Y[1], Rudan I[3], Car J[2].

Department of Integrated Early Childhood Development, Capital Institute of Pediatrics, Beijing, China.; Global eHealth Unit, Department of Primary Care and Public Health, Imperial College London, London, UK.; Centre for Population Health Sciences and Global Health Academy, University of Edinburgh Medical School, Edinburgh, UK.

OBJECTIVE:

To test the effectiveness of multiple interventions on increasing the response rate of text messaging for longitudinal data collection.

METHODS:

Our cohort included 283 caregivers of children aged 6-12 months who were participating in an anemia program in rural China. Using text messages to collect data on anemia medication adherence, we conducted a delayed randomized controlled trial to test multiple interventions (an additional four reminders; a ¥5.0 (US$0.79) credit reward for replying; and a feedback text message). After a 6-week pilot study with week 7 as the baseline measurement, we randomly allocated all participants into two groups: group 1 (n = 142) and group 2 (n = 141). During weeks 8-11, we introduced the interventions to group 1, and in weeks 12-15 the intervention was introduced to both groups. We compared the response rates between groups and explored factors affecting the response rate.

RESULTS:

During weeks 8-11, the response rates in group 1 increased and were significantly higher than in group 2 ($p<0.05$). During weeks 12-15, the response rate increased significantly in group 2 ($p>0.05$) and slightly decreased in group 1. Younger participants or participants who had children with lower hemoglobin concentration were more likely to reply ($p = 0.02$). Sending four reminders on the second day contributed to only 286 (11.7%) extra text messages.

DISCUSSION:

Our study showed that multiple interventions were effective in increasing response rate of text messaging data collection in rural China.

CONCLUSIONS:

Larger multi-site studies are needed to find the most effective way of using these interventions to allow usage of text messaging data collection for health research.

http://jamia.oxfordjournals.org/content/jaminfo/22/1/51.full.pdf

Schistosomiasis

Cochrane Database Syst Rev. 2014 Aug 6;8:CD000053. doi: 10.1002/14651858.CD000053.pub3.

Drugs for treating urinary schistosomiasis.

Kramer CV[1], Zhang F, Sinclair D, Olliaro PL.

Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK,

BACKGROUND:

Urinary schistosomiasis is caused by an intravascular infection with parasitic Schistosoma haematobium worms. The adult worms typically migrate to the venous plexus of the human

bladder and excrete eggs which the infected person passes in their urine. Chronic infection can cause substantial morbidity and long-term complications as the eggs become trapped in human tissues causing inflammation and fibrosis. We summarised evidence of drugs active against the infection. This is new edition of a review first published in 1997.

OBJECTIVES:

To evaluate the efficacy and safety of drugs for treating urinary schistosomiasis.

SEARCH METHODS:

We searched the Cochrane Infectious Diseases Group Specialized Register, MEDLINE, CENTRAL, EMBASE and LILACS and reference lists of articles up to 23 May 2014.

SELECTION CRITERIA:

Randomized controlled trials (RCTs) of antischistosomal drugs and drug combinations compared to placebo, no intervention, or each other.

DATA COLLECTION AND ANALYSIS:

Two researchers independently screened the records, extracted the data and assessed risk of bias. The primary efficacy outcomes were parasitological failure (defined as the continued presence of S. haematobium eggs in the urine at time points greater than one month after treatment), and percent reduction of egg counts from baseline. We presented dichotomous data as risk ratios (RR), and continuous data as mean difference (MD), alongside their 95% confidence intervals (CIs). Where appropriate we combined trials in meta analyses or tables. We assessed the quality of evidence using the GRADE approach.

MAIN RESULTS:

We included 30 RCTs enrolling 8165 participants in this review. Twenty-four trials were conducted in children in sub-Saharan Africa, and 21 trials were over 20 years old. Many studies were assessed as being at unclear risk of bias due to inadequate descriptions of study methods. PraziquantelOn average, a single 40 mg/kg dose of praziquantel reduced the proportion of people still excreting eggs in their urine by around 60% compared to placebo at one to two months after treatment (treatment failure: RR 0.42, 95% CI 0.29 to 0.59, 864 participants, seven trials, high quality evidence). The proportion of people cured with praziquantel varied substantially between trials, from 22.5% to 83.3%, but was higher than 60% in five of the seven trials. At one to two months following praziquantel treatment at 40 mg/kg, the mean number of schistosome eggs in the urine was reduced by over 95% in five out of six trials (678 participants, six trials, high quality evidence).Splitting praziquantel 40 mg/kg into two doses over 12 hours probably has no benefits over a single dose, and in a single trial of 220 participants the split dose caused more vomiting (RR 0.5, 95% CI 0.29 to 0.86) and dizziness (RR 0.39, 95% CI 0.16 to 0.94). MetrifonateA single dose of metrifonate 10 mg/kg reduced egg excretion (210 participants, one trial, at eight months), but was only marginally better than placebo at achieving cure at one month (RR 0.83, 95% CI 0.74 to 0.94, 142 participants, one trial). In a single trial comparing one, two and three doses, the absolute number of participants cured improved from 47% after one dose to 81% after three doses (93 participants, one trial, low quality evidence).Two small trials compared 40 mg/kg single dose praziquantel with two or three doses of 10 mg/kg metrifonate and found no clear evidence of differences in cure (metrifonate 2 x 10 mg/kg at one month: RR 1.03, 95% CI 0.8 to 1.34, 72 participants, one trial; metrifonate 3 x 10 mg/kg at three months: RR 0.33, 95% CI 0.07 to 1.57, 100 participants, one trial. In one trial both drugs performed badly and in one trial both performed well. Other drugsThree trials have evaluated the antimalarial artesunate; with inconsistent results. Substantial antischistosomal

effects were only seen in one of the three trials, which was at unclear risk of bias due to poor reporting of the trial methods. Similarly, another anti-malarial mefloquine has been evaluated in two small trials with inconsistent effects.Adverse events were described as mild for all evaluated drugs, but adverse event monitoring and reporting was generally of low quality.

AUTHORS' CONCLUSIONS:

Praziquantel 40 mg/kg is the most studied drug for treating urinary schistosomiasis, and has the strongest evidence base.Potential strategies to improve future treatments for schistosomiasis include the combination of praziquantel with metrifonate, or with antimalarial drugs with antischistosomal properties such as artesunate and mefloquine. Evaluation of these combinations requires rigorous, adequately powered trials using standardized outcome measures.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4447116/pdf/CD000053-0001.pdf

Trans R Soc Trop Med Hyg. 2014 Sep;108(9):575-81. doi: 10.1093/trstmh/tru097. Epub 2014 Jul 24.

Mass drug administration with praziquantel reduces the prevalence of Schistosoma mansoni and improves liver morbidity in untreated preschool children.

Cleland CR[1], Tukahebwa EM[2], Fenwick A[3], Blair L[3].

Schistosomiasis Control Initiative, Department of Infectious Disease Epidemiology, Imperial College London, UK; Vector Control Division, Ministry of Health, Kampala, Uganda.

BACKGROUND:

The aim of this study was to investigate the effects of mass drug administration on Schistosoma mansoni prevalence and associated liver morbidity in treated school-aged children and untreated preschool children.

METHODS:

In April 2008, parasitological (using the Kato-Katz method) and morbidity (determined by portal vein score) data were collected from 263 schoolchildren aged 6 and 7 years. The children had never received praziquantel. In March 2010, following two annual rounds of mass drug administration, 207 children aged 8 and 9 years old were examined to determine the effect of treatment. In addition, 158 untreated 6-year-olds were assessed to compare with the untreated children from 2008.

RESULTS:

Treatment significantly decreased the prevalence of S. mansoni and associated morbidity in the treated groups. The untreated preschool children also showed a significant decrease in the prevalence of S. mansoni, from 21.1% (2008) to 6.3% (2010) ($p<0.001$). The percentage of untreated schoolchildren with a normal portal vein score increased significantly from 57.8% (2008) to 70.3% (2010) ($p=0.029$).

CONCLUSION:

The significantly lower rates of S. mansoni and the decreased liver morbidity in untreated preschool children in 2010 suggest decreased environmental transmission rates and improved liver morbidity in untreated children following several rounds of mass drug administration.

PLoS Negl Trop Dis. 2015 May 26;9(5):e0003796. doi: 10.1371/journal.pntd.0003796. eCollection 2015.

Single Versus Double Dose Praziquantel Comparison on Efficacy and Schistosoma mansoni Re-Infection in Preschool-Age Children in Uganda: A Randomized Controlled Trial.

Nalugwa A[1], Nuwaha F[2], Tukahebwa EM[3], Olsen A[4].

Child Health and Development Centre, Makerere University, Kampala, Uganda.; Disease Control and Prevention, Makerere University, Kampala, Uganda.; Vector Control Division, Ministry of Health, Kampala, Uganda ; Department of Veterinary Disease Biology, University of Copenhagen, Frederiksberg, Denmark.

BACKGROUND:

Schistosoma mansoni infection is proven to be a major health problem of preschool-age children in sub-Saharan Africa, yet this age category is not part of the schistosomiasis control program. The objective of this study was to compare the impact of single and double dose praziquantel (PZQ) treatment on cure rates (CRs), egg reduction rates (ERRs) and re-infection rates 8 months later, in children aged 1-5 years living along Lake Victoria, Uganda.

METHODOLOGY/PRINCIPAL FINDINGS:

Infected children (n= 1017) were randomized to receive either a single or double dose of PZQ. Initially all children were treated with a single standard oral dose 40 mg/kg body weight of PZQ. Two weeks later a second dose was administered to children in the double dose treatment arm. Side effects were monitored at 30 minutes to 24 hours after each treatment. Efficacy in terms of CRs and ERRs for the two treatments was assessed and compared 1 month after the second treatment. Re-infection with S. mansoni was assessed in the same children 8 months following the second treatment. CRs were non-significantly higher in children treated with two 40 mg/kg PZQ doses (85.5%; 290/339) compared to a single dose (83.2%; 297/357). ERRs were significantly higher in the double dose with 99.3 (95%CI: 99.2-99.5) compared with 98.9 (95%CI: 98.7-99.1) using a single dose, (P = 0.01). Side effects occurred more frequently during the first round of drug administration and were mild and short-lived; these included vomiting, abdominal pain and bloody diarrhea. Overall re-infection rate 8 months post treatment was 44.5%.

CONCLUSIONS:

PZQ is efficacious and relatively safe to use in preschool-age children but there is still an unmet need to improve its formulation to suit small children. Two PZQ doses lead to significant reduction in egg excretion compared to a single dose. Re-infection rates with S. mansoni 8 months post treatment is the same among children irrespective of the treatment regimen.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4444284/pdf/pntd.0003796.pdf

Am J Trop Med Hyg. 2014 Nov;91(5):973-81. doi: 10.4269/ajtmh.14-0328. Epub 2014 Sep 22.

Efficacy and safety of arachidonic acid for treatment of Schistosoma mansoni-infected children in Menoufiya, Egypt.

Selim S[1], El Sagheer O[1], El Amir A[1], Barakat R[1], Hadley K[1], Bruins MJ[1], El Ridi R[2].

Department of Parasitology, National Liver Institute, Menoufiya University, Shebin El-Kom, Menoufiya, Egypt; Zoology Department, Faculty of Science, Cairo University, Cairo, Egypt; Tropical Health Department, High Institute of Public Health, Alexandria University, Alexandria, Egypt; Human Evidence Department, DSM North America, Columbia, Maryland; Research and Development Department, DSM Biotechnology Center, Delft, The Netherlands.; Department of Parasitology, National Liver Institute, Menoufiya University, Shebin El-Kom, Menoufiya, Egypt; Zoology Department, Faculty of Science, Cairo University, Cairo, Egypt; Tropical Health Department, High Institute of Public Health, Alexandria University, Alexandria, Egypt; Human Evidence Department, DSM North America, Columbia, Maryland; Research and Development Department, DSM Biotechnology Center, Delft, The Netherlands rashika@mailer.eun.eg.

Abstract

Arachidonic acid (ARA), an omega-6 fatty acid, kills juvenile and adult schistosomes in vitro and displays highly significant and safe therapeutic effects in mice and hamsters infected with Schistosoma mansoni or S. haematobium. This study aims to examine the efficacy and safety of ARA in treatment of school-age children infected with S. mansoni. In total, 66 S. mansoni-infected schoolchildren (20-23 children/study arm) received a single dose of 40 mg/kg praziquantel (PZQ), ARA (10 mg/kg per day for 15 days), or PZQ combined with ARA. The children were examined before and after treatment for worm egg counts in stool and blood biochemical and immunological parameters. ARA proved to be as efficacious as PZQ in treatment of schoolchildren with low infection intensity (78% and 85% cure rates, respectively). For moderate-intensity infection, the ARA and PZQ combination led to 100% cure rate. Biochemical, hematological, and immunological parameters were either unchanged or ameliorated after ARA therapy.

Int J Parasitol. 2014 Aug;44(9):659-68. doi: 10.1016/j.ijpara.2014.05.005. Epub 2014 Jun 11.

A multi-component integrated approach for the elimination of schistosomiasis in the People's Republic of China: design and baseline results of a 4-year cluster-randomised intervention trial.

Gray DJ[1], Li YS[2], Williams GM[3], Zhao ZY[4], Harn DA[5], Li SM[4], Ren MY[4], Feng Z[6], Guo FY[4], Guo JG[4], Zhou J[4], Dong YL[4], Li Y[7], Ross AG[8], McManus DP[9].

Molecular Parasitology Laboratory, Infectious Diseases Division, QIMR Berghofer Medical Research Institute, Brisbane, Australia; School of Population Health, University of Queensland, Brisbane, Australia; Research School of Population Health, Australian National University, Canberra, Australia.; Molecular Parasitology Laboratory, Infectious Diseases Division, QIMR Berghofer Medical Research Institute, Brisbane, Australia; Hunan Institute of Parasitic Diseases, World Health Organisation Collaborating Centre for Research ;

Control of Schistosomiasis in Lake Region, Yueyang, Hunan Province, People's Republic of China.; School of Population Health, University of Queensland, Brisbane, Australia.; Hunan Institute of Parasitic Diseases, World Health Organisation Collaborating Centre for Research and Control of Schistosomiasis in Lake Region, Yueyang, Hunan Province, People's Republic of China.; Department of Infectious Diseases, College of Veterinary Medicine and Center for Tropical and Emerging Global Diseases, University of Georgia, Athens, USA; National Institute of Parasitic Diseases, Chinese Centre for Disease Control and Prevention, Shanghai, People's Republic of China.; Central South University, Changsha, People's Republic of China.; Griffith

Health Institute, Griffith University, Gold Coast, Australia.; Molecular Parasitology Laboratory, Infectious Diseases Division, QIMR Berghofer Medical Research Institute, Brisbane, Australia.

Abstract

Despite major successes in its control over the past 50years, schistosomiasis japonica continues to be a public health problem in the People's Republic of China (P.R. China). Historically, the major endemic foci occur in the lakes and marshlands along the Yangtze River, areas where transmission interruption has proven difficult. The current endemic situation may alter due to the closure of the Three Gorges Dam. Considerable environmental and ecological changes are anticipated that may result in new habitats for the oncomelanid intermediate snail host of Schistosoma japonicum (Sj), thereby increasing the risk of transmission. The current national control program for P.R. China involves a multi-component integrated strategy but, despite targeting multiple transmission pathways, certain challenges remain. As the Chinese government pushes towards elimination, there is a requirement for additional tools, such as vaccination, for long-term prevention. Whereas the zoonotic nature of schistosomiasis japonica adds to the complexity of control, it provides a unique opportunity to develop a transmission blocking vaccine targeting bovines to assist in the prevention of human infection and disease. Mathematical modelling has shown that control options targeting the various transmission pathways of schistosomiasis japonica and incorporating bovine vaccination, mass human chemotherapy and molluscicide could lead to its elimination from P.R. China. Here we present the study design and baseline results of a four-year cluster randomised intervention trial we are undertaking around the schistosomiasis-endemic Dongting Lake in Hunan Province aimed at determining the impact on schistosome transmission of the multi-component integrated control strategy, including bovine vaccination using a heterologous "prime-boost" delivery platform based on the previously tested SjCTPI vaccine.

School health and education

(See Adolescent health)

Indian J Pediatr. 2015 Apr;82(4):354-62. doi: 10.1007/s12098-014-1562-9. Epub 2014 Sep 12.

Effectiveness of a school based intervention for prevention of non-communicable diseases in middle school children of rural North India: a randomized controlled trial.

Saraf DS[1], Gupta SK, Pandav CS, Nongkinrih B, Kapoor SK, Pradhan SK, Krishnan A.

Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi,India,

OBJECTIVE:

To assess the effectiveness of a multi-component school based intervention in improving knowledge and behavioral practices regarding diet, physical activity and tobacco use in middle schoolchildren of rural-Ballabgarh, North-India.

METHODS:

A total of 40 middle schools were grouped into two, based on geographic proximity and randomly assigned to the intervention or control group in a cluster randomized controlled trial. The target population consisted of 2,348 children studying in 6th and 7th grades in these schools. The intervention consisted of a school component (policies), a classroom component (activities) and a family component [Information Education & Communication (IEC) material]. The main outcome measures were knowledge and behavioral changes in physical activity, diet and tobacco which were self- reported.

RESULTS:

Post-intervention, a significant number of intervention schools adopted the tobacco policy (16/19), physical activity policy (6/19) and healthy food policy (14/19) as compared to the control schools (n = 21). Knowledge about physical activity, diet and tobacco improved significantly in the intervention group as compared to the control group. Proportion of students attending Physical Training (PT) classes for five or more days in a week in the intervention group compared to the control group increased significantly (17.8%; $p < 0.01$). Proportion of students consuming fruits increased in the intervention group compared to the control group (10%; $p < 0.01$). Pre-post decrease in the prevalence of current smoking was significantly more in the intervention group as compared to the control group (7.7%; $p < 0.01$).

CONCLUSIONS:

Healthy settings approach for schools is feasible and effective in improving knowledge and behavioral practices of non-communicable diseases (NCD) risk factors in adolescents in rural India.

Indian J Public Health. 2014 Oct-Dec;58(4):235-40. doi: 10.4103/0019-557X.146278.

Oral health promotion among rural school children through teachers: an interventional study.

Chandrashekar BR[1], Suma S, Sukhabogi JR, Manjunath BC, Kallury A.

Reader, Department of Public Health Dentistry, People's Dental Academy, Bhanpur, Bhopal, India.

BACKGROUND:

The lack of national oral health policy and organized school dental health programs in the country call for affordable, accessible, and sustainable strategies.

OBJECTIVES:

The objective was to compare the oral hygiene, plaque, gingival, and dental caries status among rural children receiving dental health education by qualified dentists and school teachers with and without supply of oral hygiene aids.

MATERIALS AND METHODS:

This interventional study was conducted among 15-year-old children selected randomly from four schools in Nalgonda district between September 2009 and February 2010. Schools were

divided into four different intervention groups. The intervention groups varied in the form of intervention provider and frequency of intervention one of which being the control group. The oral hygiene, plaque, gingival, and dental caries status was assessed at baseline and 6 months following the intervention. SPSS 16 was used for analysis.

RESULTS:

The preintervention and postintervention comparison within each group revealed a substantial reduction in mean oral hygiene index-simplified (OHI-S), plaque index (PI), and gingival index (GI) at postintervention compared to baseline in group 4 (1.26, 0.87, and 0.74, respectively) followed by group 3 (0.14, 0.37, and 0.12, respectively). The OHI-S, PI, and GI scores increased in group 1 (0.66, 0.37, and 0.34, respectively) and group 2 (0.25, 0.19, and 0.14, respectively). Mean decayed, missing filled surfaces score between the groups was not statistically significant at baseline and postintervention.

CONCLUSION:

The dramatic reductions in the OHI-S, PI, and GI scores in the group supplied with oral hygiene aids call for supplying low cost fluoridated toothpastes along with toothbrushes through the school systems in rural areas.

BMJ. 2015 Mar 18;350:h770. doi: 10.1136/bmj.h770.

School based education programme to reduce salt intake in children and their families (School-EduSalt): cluster randomised controlled trial.

He FJ[1], Wu Y[2], Feng XX[3], Ma J[4], Ma Y[5], Wang H[4], Zhang J[6], Yuan J[3], Lin CP[7], Nowson C[8], MacGregor GA[9].

Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK ; George Institute for Global Health at Peking University Health Science Center, Beijing, China Department of Epidemiology and Biostatistics, Peking University School of Public Health, Beijing, China Peking University Clinical Research Institute, Beijing, China.; Changzhi Medical College, Shanxi, China.; Institute of Child and Adolescent Health, Peking University Health Science Center, Beijing, China.; George Institute for Global Health at Peking University Health Science Center, Beijing, China University of Michigan Medical School, Ann Arbor, MI, USA.; School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia.

OBJECTIVE:

To determine whether an education programme targeted at schoolchildren could lower salt intake in children and their families.

DESIGN:

Cluster randomised controlled trial, with schools randomly assigned to either the intervention or control group.

SETTING:

28 primary schools in urban Changzhi, northern China.

PARTICIPANTS:

279 children in grade 5 of primary school, with mean age of 10.1; 553 adult family members (mean age 43.8).

INTERVENTION:

Children in the intervention group were educated on the harmful effects of salt and how to reduce salt intake within the schools' usual health education lessons. Children then delivered the salt reduction message to their families. The intervention lasted for one school term (about 3.5 months).

MAIN OUTCOME MEASURES:

The primary outcome was the difference between the groups in the change in salt intake (as measured by 24 hour urinary sodium excretion) from baseline to the end of the trial. The secondary outcome was the difference between the two groups in the change in blood pressure.

RESULTS:

At baseline, the mean salt intake in children was 7.3 (SE 0.3) g/day in the intervention group and 6.8 (SE 0.3) g/day in the control group. In adult family members the salt intakes were 12.6 (SE 0.4) and 11.3 (SE 0.4) g/day, respectively. During the study there was a reduction in salt intake in the intervention group, whereas in the control group salt intake increased. The mean effect on salt intake for intervention versus control group was -1.9 g/day (95% confidence interval -2.6 to -1.3 g/day; P<0.001) in children and -2.9 g/day (-3.7 to -2.2 g/day; P<0.001) in adults. The mean effect on systolic blood pressure was -0.8 mm Hg (-3.0 to 1.5 mm Hg; P=0.51) in children and -2.3 mm Hg (-4.5 to -0.04 mm Hg; P<0.05) in adults.

CONCLUSIONS:

An education programme delivered to primary school children as part of the usual curriculum is effective in lowering salt intake in children and their families. This offers a novel and important approach to reducing salt intake in a population in which most of the salt in the diet is added by consumers.Trial registration ClinicalTrials.gov NCT01821144. .

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364292/pdf/bmj.h770.pdf

Trials. 2014 Dec 1;15:471. doi: 10.1186/1745-6215-15-471.

Implementing an early childhood school-based mental health promotion intervention in low-resource Ugandan schools: study protocol for a cluster randomized controlled trial.

Huang KY[1], Nakigudde J, Calzada E, Boivin MJ, Ogedegbe G, Brotman LM.

Department of Population Health, New York University Langone Medical Center, New York, NY, USA.

BACKGROUND:

Children in Sub-Saharan Africa (SSA) are burdened by significant unmet mental health needs, but this region has limited access to mental health workers and resources to address these needs. Despite the successes of numerous school-based interventions for promoting child mental

health, most evidence-based interventions are not available in SSA. This study will investigate the transportability of an evidence-based program from a developed country (United States) to a SSA country (Uganda). The approach includes task-shifting to early childhood teachers and consists of professional development (five days) to introduce strategies for effective behavior management and positive teacher-student interactions, and group-based consultation (14 sessions) to support adoption of effective practices and tailoring to meet the needs of individual students.

METHODS/DESIGN:

The design of this study is guided by two implementation frameworks, the Consolidated Framework for Implementation Research and the Teacher Training Implementation Model, that consider multidimensional aspects of intervention fidelity and contextual predictors that may influence implementation and teacher outcomes. Using a cluster randomized design, 10 schools in Uganda will be randomized to either the intervention group (five schools) or the waitlist control group (five schools). A total of 80 to 100 early childhood teachers will be enrolled in the study. Teacher utilization of evidence-based strategies and practices will be assessed at baseline, immediate post-intervention (six months after baseline), and at seven months post-intervention (during a new academic year). Fidelity measures will be assessed throughout the program implementation period (during professional development and consultation sessions). Individual teacher and contextual factors will be assessed at baseline. Data will be collected from multiple sources. Linear mixed-effect modeling, adjusting for school nesting, will be applied to address study questions.

DISCUSSION:

The study will produce important information regarding the value of an evidence-based early intervention, and a theory-guided implementation process and tools designed for use in implementing early childhood evidence-based programs in SSA countries or resource-constrained community settings.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4289288/pdf/13063_2014_Article_2336.pdf

Res Dev Disabil. 2014 Jul;35(7):1648-57. doi: 10.1016/j.ridd.2014.03.024. Epub 2014 Apr 25.

The effect of computer-assisted therapeutic practice for children with handwriting deficit: a comparison with the effect of the traditional sensorimotor approach.

Chang SH[1], Yu NY[2].

Department of Physical Therapy, I-Shou University, Taiwan.; Department of Physical Therapy, I-Shou University Taiwan.

Abstract

The objective of this study was to compare the effect of computer-assisted practice with the sensorimotor approach on the remediation of handwriting problems in children with dysgraphia. In a randomized controlled trial, experiments were conducted to verify the intervention effect. Forty two children with handwriting deficit were assigned to computer-assisted instruction, sensorimotor training, or a control group. Handwriting performance was measured using the elementary reading/writing test and computerized handwriting evaluation before and after 6 weeks of intervention. Repeated-measures ANOVA of changed scores were conducted to show

whether statistically significant differences across the three groups were present. Significant differences in the elementary reading/writing test were found among the three groups. The computer group showed more significant improvements than the other two groups did. In the kinematic and kinetic analyses, the computer group showed promising results in the remediation of handwriting speed and fluency. This study provided clinical evidence for applying a computer-assisted handwriting program for children with dysgraphia. Clinicians and school teachers are provided with a systematic intervention for the improvement of handwriting difficulties.

Skin and hair disease

PLoS Negl Trop Dis. 2014 Jul 31;8(7):e3058. doi: 10.1371/journal.pntd.0003058. eCollection 2014.

Treatment of Tungiasis with dimeticone: a proof-of-principle study in rural Kenya.

Thielecke M[1], Nordin P[2], Ngomi N[3], Feldmeier H[1].

Institute of Microbiology and Hygiene, Campus Benjamin Franklin, Charité University Medicine, Berlin, Germany.; Skaraborg Institute for Research and Development, Skövde, Sweden.; African Population and Health Research Center, Nairobi, Kenya.

Abstract

Tungiasis (sand flea disease) is a neglected tropical disease, prevalent in resource-poor communities in South America and sub-Saharan Africa. It is caused by an inflammatory response against penetrated female sand fleas (Tunga penetrans) embedded in the skin of the host. Although associated with debilitating acute and chronic morbidity, there is no proven effective drug treatment. By consequence patients attempt to remove embedded sand fleas with non-sterile sharp instruments, such as safety pins, a procedure that represents a health threat by itself. In this proof-of-principle study we compared the topical application of a mixture of two dimeticones of low viscosity (NYDA) to the topical application of a 0.05% solution of KMnO4 in 47 school children in an endemic area in rural Kenya. The efficacy of the treatment was assessed during a follow up period of seven days using viability signs of the embedded parasites, alterations in the natural development of lesion morphology and the degree of local inflammation as outcome measures. Seven days after treatment, in the dimeticone group 78% (95% CI 67-86%) of the parasites had lost all signs of viability as compared to 39% (95% CI 28-52%) in the KMnO4 group ($p<0.001$). In the dimeticone group 90% (95% CI 80-95%) of the penetrated sand fleas showed an abnormal development already after 5 days, compared to 53% (95% CI 40-66%; $p<0.001$) in the KMnO4 group. Seven days after treatment, signs of local skin inflammation had significantly decreased in the dimeticone group ($p<0.001$). This study identified the topical application of dimeticones of low viscosity (NYDA) as an effective means to kill embedded sand fleas. In view of the efficacy and safety of the topical treatment with dimeticone, the mechanical extraction of embedded sand fleas using hazardous instruments is no longer warranted.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4117482/pdf/pntd.0003058.pdf

Pediatrics. 2015 Apr;135(4):597-606. doi: 10.1542/peds.2014-1990. Epub 2015 Mar 23.

Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial.

Sigurgeirsson B[1], Boznanski A[2], Todd G[3], Vertruyen A[4], Schuttelaar ML[5], Zhu X[6], Schauer U[7], Qaqundah P[8], Poulin Y[9], Kristjansson S[10], von Berg A[11], Nieto A[12], Boguniewicz M[13], Paller AS[14], Dakovic R[15], Ring J[16], Luger T[17].

Faculty of Medicine, Department of Dermatology, University of Iceland, Reykjavik, Iceland; Department of Children Allergology and Cardiology, Wroclaw Medical University, Wroclaw, Poland; Department of Medicine, University of Cape Town, Cape Town, South Africa; GZA Campus Sint-Vincentius, Antwerpen, Belgium; Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Department of Dermatology, Peking University First Hospital, Beijing, China; Klinik für Kinder und Jugendmedizin, der Ruhruniversität Bochum, Bochum, Germany;

Pediatric Care Medical Group, Huntington Beach, California, and University of California, Irvine, California; Laval University Quebec City, Canada; Department of Pediatrics, Landspitali-University Hospital, Reykjavik, Iceland; Research Institute, Children's Department, Marien-Hospital-Wesel, Wesel, Germany;; Pediatric Pulmonology & Allergy Unit, Children's Hospital La Fe, Valencia, Spain; Division of Pediatric Allergy-Immunology, Department of Pediatrics, National Jewish Health and University of Colorado School of Medicine, Denver, Colorado; Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois; Meda Pharma GmbH & Co. KG, Bad Homburg, Germany; Department of Dermatology and Allergology Biederstein, Christine Kühne-Center for Allergy Research and Education, Technische Universität München, Munich, Germany; Department of Dermatology, University of Münster, Münster, Germany.

BACKGROUND AND OBJECTIVES:

Atopic dermatitis (AD) primarily affects infants and young children. Although topical corticosteroids (TCSs) are often prescribed, noncorticosteroid treatments are needed because compliance with TCSs is poor due to concerns about their side effects. In this longest and largest intervention study ever conducted in infants with mild-to-moderate AD, pimecrolimus 1% cream (PIM) was compared with TCSs.

METHODS:

A total of 2418 infants were enrolled in this 5-year open-label study. Infants were randomized to PIM (n = 1205; with short-term TCSs for disease flares) or TCSs (n = 1213). The primary objective was to compare safety; the secondary objective was to document PIM's long-term efficacy. Treatment success was defined as an Investigator's Global Assessment score of 0 (clear) or 1 (almost clear).

RESULTS:

Both PIM and TCSs had a rapid onset of action with >50% of patients achieving treatment success by week 3. After 5 years, >85% and 95% of patients in each group achieved overall and facial treatment success, respectively. The PIM group required substantially fewer steroid days than the TCS group (7 vs 178). The profile and frequency of adverse events was similar in the 2 groups; in both groups, there was no evidence for impairment of humoral or cellular immunity.

CONCLUSIONS:

Long-term management of mild-to-moderate AD in infants with PIM or TCSs was safe without any effect on the immune system. PIM was steroid-sparing. The data suggest PIM had similar

efficacy to TCS and support the use of PIM as a first-line treatment of mild-to-moderate AD in infants and children.

Parasitol Res. 2014 Sep;113(9):3241-50. doi: 10.1007/s00436-014-3986-6. Epub 2014 Jun 20.

Efficacy of herbal shampoo base on native plant against head lice (Pediculus humanus capitis De Geer, Pediculidae: Phthiraptera) in vitro and in vivo in Thailand.

Soonwera M[1].

Plant Production Technology Section, Faculty of Agricultural Technology, King Mongkut's Institute of Technology Ladkrabang, Ladkrabang, Bangkok, Thailand.

Abstract

Head lice infestation (or pediculosis) is an important public health problem in Thailand, especially in children between the ages 5 and 11 years. Head lice resistance is increasing, chemical pediculicides have lost their efficacy, and, therefore, alternative pediculicides such as herbal shampoos have been proposed to treat head lice infestation. Thus, the present study investigated the efficacy of three herbal shampoos based on native plants in Thailand (Acorus calamus Linn., Phyllanthus emblica Linn., and Zanthoxylum limonella Alston) against head lice and compared them with carbaryl shampoo (Hafif shampoo, 0.6% w/v carbaryl), malathion shampoo (A-Lice shampoo, 1.0% w/v malathion), and commercial shampoos (Babi Mild Natural' N Mild and Johnson's baby shampoo) in order to assess their in vitro and in vivo efficacy. For in vitro study, doses of 0.12 and 0.25 ml/cm(2) of each herbal shampoo were applied to filter paper, then 10 head lice were place on the filter paper. The mortalities of head lice were recorded at 5, 15, 30, and 60 min. The results revealed that all herbal shampoo were more effective on pediculicidal activity than chemical and commercial shampoos with 100% mortality at 15 min; LT_{50} values ranged from 0.25 to 1.90 min. Meanwhile, chemical shampoos caused 20-80% mortality, and LT_{50} values ranged from 6.50 to 85.43 min. On the other side, commercial shampoos showed 4.0% mortality. The most effective pediculicide was Z. limonella shampoo, followed by A. calamus shampoo, P. emblica shampoo, carbaryl shampoo, malathion shampoo, and commercial shampoo, respectively. In vivo results showed that all herbal shampoos were also more effective for head lice treatment than chemical and commercial shampoos with 94.67-97.68% of cure rate after the first treatment; the second treatment, 7 days later, revealed that the cure rate was 100%. Meanwhile, chemical shampoo showed 71.67-93.0% of cure rate and, unfortunately, commercial shampoos were nontoxic to head lice and showed 0% of cure rate after the first and the second treatments. Our data showed that three herbal shampoos of native plants in Thailand in this study are suitable to be used as pediculicides for Thai children since it is safe for children and there is no side-effect after application.

Dermatol Ther. 2014 Sep-Oct;27(5):272-7. doi: 10.1111/dth.12136. Epub 2014 Jun 9.

Evaluation of TNF-α serum level in patients with recalcitrant multiple common warts, treated by lipid garlic extract.

Kenawy S[1], Mohammed GF, Younes S, Elakhras AI.

Department of Dermatology and Venereology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

Abstract

No universal consensus about optimal modality for treating the recalcitrant multiple common warts (RMCW). The objective of the study was to evaluate the immunological mechanisms and clinical therapeutic effect of using lipid garlic extract (LGE) in the treatment of RMCW. The study included 50 patients with RMCW. They were randomly assigned into two groups: the first group (25 patients) received LGE, and the second group (25 patients) received saline as a control group. In both groups, treatments were made to single lesions, or largest wart in case of multiple lesions, until complete clearance of lesions or for a maximum of 4 weeks. Blood serum was taken at pre-study and at the fourth week to measure tumor necrosis factor alpha (TNF-α) level. A significant difference was found between the therapeutic responses of RMCW to LGE antigen and saline control group ($p < 0.001$). In the LGE group, complete response was achieved in 96% of patients presenting with RMCW. There was a statistically nonsignificant increase in TNF-α of LGE group versus saline group. No recurrence was observed in the LGE group. LGE as an immunotherapy is an inexpensive, effective, and safe modality with good cure rates for treatment of RMCWs, when other topical or physical therapies have failed.

Surgical problems

Vaccine. 2014 Aug 11;32 Suppl 1:A99-103. doi: 10.1016/j.vaccine.2014.03.028.

Intussusception in southern India: comparison of retrospective analysis and active surveillance.

Jehangir S[1], John J[2], Rajkumar S[3], Mani B[4], Srinivasan R[3], Kang G[5].

Department of Pediatric Surgery, Christian Medical College, Vellore, India.; Department of Community Health, Christian Medical College, Vellore, India.; Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India.; Department of Radiology, Christian Medical College, Vellore, India.; Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India. Electronic address:

Abstract

Surveillance for intussusception is a post marketing requirement for rotavirus vaccines following observation of a small increased risk of intussusception after rotavirus vaccination in some global settings. This study presents the clinical presentation and outcomes of children who presented with intussusception at a large tertiary care facility directly (non-surveillance) as retrospective analysis of a period where rotavirus vaccine was not in routine use, or as part of active surveillance in a phase III oral rotavirus vaccine trial. Hospital records of children under 2 years of age treated for intussusception between 1 January 2010 and 31 August 2013 at the Christian Medical College Hospital, Vellore, India, were reviewed. Sixty-one cases of intussusception in children under two years of age presented at the hospital. An additional 16 cases of ultrasound diagnosed intussusception were identified through the active surveillance of a cohort of 1500 children participating in a rotavirus phase III trial in the same period. In the nonsurveillance group, median age at presentation was 214 days (IQR 153-321) with 52 events (85.3%) occurring in the first year of life. Cases were seen year-round with no definitive

evidence of seasonality. Thirty-one (50.8%) intussusceptions required surgical reduction, 26 (42.6%) had pneumatic reduction and 2 (3.3%) barium enema reduction. Two intussusceptions (3.3%) resolved spontaneously. There were no deaths, all children were discharged after recovery. Active surveillance identified 16 children with a median age at event of 375 days (IQR 248-574). Nine (56%) children had small bowel or transient intussusception that resolved spontaneously. Seven intussusceptions were reduced radiologically; none required surgery. In summary, there were significant differences between presentation and outcomes in cases of intussusception identified by passive and active surveillance, likely related to enhanced and early detection of intussusception through active monitoring in the trial. The WHO recommendation of sentinel hospital based surveillance for post-marketing surveillance after rotavirus vaccine introduction is likely to a better approach than active surveillance.

J Craniomaxillofac Surg. 2015 Apr 10. pii: S1010-5182(15)00087-6. doi: 10.1016/j.jcms.2015.03.033. [Epub ahead of print]

A randomized controlled trial comparing two techniques for unilateral cleft lip and palate: Growth and speech outcomes during mixed dentition.

Ganesh P[1], Murthy J[2], Ulaghanathan N[3], Savitha VH[3].

Department of Cranio-Maxillofacial Surgery, Mazumdar Shaw Medical Center, Narayana Health City, Bommasandra, Bangalore, Karnataka, India ;Department of Plastic and Reconstructive Surgery, Sri Ramachandra University, Chennai, India.; Department of Speech, Language & Hearing Sciences, Sri Ramachandra University, Chennai, India.

OBJECTIVE:

To study the growth and speech outcomes in children who were operated on for unilateral cleft lip and palate (UCLP) by a single surgeon using two different treatment protocols.

MATERIAL AND METHODS:

A total of 200 consecutive patients with nonsyndromic UCLP were randomly allocated to two different treatment protocols. Of the 200 patients, 179 completed the protocol. However, only 85 patients presented for follow-up during the mixed dentition period (7-10 years of age).
The following treatment protocol was followed. Protocol 1 consisted of the vomer flap (VF), whereby patients underwent primary lip nose repair and vomer flap for hard palate single-layer closure, followed by soft palate repair 6 months later; Protocol 2 consisted of the two-flap technique (TF), whereby the cleft palate (CP) was repaired by two-flap technique after primary lip and nose repair. GOSLON Yardstick scores for dental arch relation, and speech outcomes based on universal reporting parameters, were noted.

RESULTS:

A total of 40 patients in the VF group and 45 in the TF group completed the treatment protocols. The GOSLON scores showed marginally better outcomes in the VF group compared to the TF group. Statistically significant differences were found only in two speech parameters, with better outcomes in the TF group.

CONCLUSIONS:

Our results showed marginally better growth outcome in the VF group compared to the TF group. However, the speech outcomes were better in the TF group.

Int Orthop. 2014 Sep;38(9):1987-92. doi: 10.1007/s00264-014-2361-7. Epub 2014 May 15.

Effectiveness of recombinant human bone morphogenetic protein-7 in the management of congenital pseudoarthrosis of the tibia: a randomised controlled trial.

Das SP[1], Ganesh S, Pradhan S, Singh D, Mohanty RN.

Department of PM&R, SVNIRTAR, Olatpur,., Odisha, India,

PURPOSE:

Despite the popularity and an increased use of bone morphogenetic protein to improve bone healing in patients with congenital pseudoarthrosis of the tibia (CPT), no previous study has compared its efficacy against any other procedure.

METHODS:

We randomised 20 consecutive patients (mean age 4.1 years) with CPT (Crawford type IV) associated with neurofibromatosis type 1(NF1) and no previous history of surgery into two groups. Group 1 received recombinant human bone morphogenetic protein-7 (rhBMP-7) along with intramedullary Kirschner (K)-wire fixation and autologous bone grafting; group 2 received only K wire and grafting. Outcome measures were time to achieve union, Johnston grade, tibial length and the American Orthopaedic Foot and Ankle Society (AOFAS) score, which were evaluated preoperatively and at five year follow-up.

RESULTS:

Study results showed that patients in group 1 achieved primary bone union at a mean of 14.5 months [standard error (SE) 5.2], whereas group 2 took a mean of 17.11 months (SE 5.0). However, the log-rank test showed no difference in healing times between groups at all time points ($P = 0.636$). There was a statistically significant pre- to post operative improvement ($P < 0.05$) within groups for the other outcome measures.

CONCLUSION:

In a five year follow-up, these results suggest that rh-BMP-7 and autologous bone grafting is no better than autologous grafting alone.

Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

Lancet. 2015 May 2;385(9979):1738-47. doi: 10.1016/S0140-6736(14)62002-X. Epub 2015 Mar 18.

Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis.

Randomised trials in child health in developing countries 2014-15

Dawson R[1], Diacon AH[2], Everitt D[3], van Niekerk C[4], Donald PR[5], Burger DA[6], Schall R[6], Spigelman M[7], Conradie A[4], Eisenach K[8], Venter A[9], Ive P[10], Page-Shipp L[11], Variava E[12], Reither K[13], Ntinginya NE[14], Pym A[15], von Groote-Bidlingmaier F[16], Mendel CM[7].

Division of Pulmonology and Department of Medicine, University of Cape Town Lung Institute, Mowbray, Cape Town, South Africa.;Division of Physiology, Department of Medical Biochemistry, Stellenbosch University, Tygerberg, South Africa; TASK Applied Science, Bellville, South Africa.;Global Alliance for TB Drug Development, New York, NY, USA. ; Global Alliance for TB Drug Development, Pretoria, South Africa.; Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg, South Africa.; Department of Mathematical Statistics and Actuarial Science, University of the Free State, Bloemfontein, South Africa; Quintiles Biostatistics, Bloemfontein, South Africa.; Global Alliance for TB Drug Development, New York, NY, USA.; Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR, USA.; MRC Centre for Tuberculosis Research, Stellenbosch University, Tygerberg, South Africa; Task Applied Science, Tygerberg, South Africa.; Clinical HIV Research Unit, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.; Aurum Institute, Parktown, Johannesburg, South Africa.; Klerksdorp Tshepong Hospital Complex, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.; Swiss Tropical and Public Health Institute, Basel, Switzerland; Ifakara Health Institute, Bagamoyo, Tanzania.; NIMR-Mbeya Medical Research Centre, Mbeya, Tanzania.; KwaZulu-Natal Research Institute for Tuberculosis & HIV, Nelson R Mandela School of Medicine, Durban, South Africa.; TASK Applied Science, Bellville, South Africa.

BACKGROUND:

New antituberculosis regimens are urgently needed to shorten tuberculosis treatment. Following on from favourable assessment in a 2 week study, we investigated a novel regimen for efficacy and safety in drug-susceptible and multidrug-resistant (MDR) tuberculosis during the first 8 weeks of treatment.

METHODS:

We did this phase 2b study of bactericidal activity--defined as the decrease in colony forming units (CFUs) of Mycobacterium tuberculosis in the sputum of patients with microscopy smear-positive pulmonary tuberculosis-at eight sites in South Africa and Tanzania. We enrolled treatment-naive patients with drug-susceptible, pulmonary tuberculosis, who were randomly assigned by computer-generated sequences to receive either 8 weeks of moxifloxacin, 100 mg pretomanid (formerly known as PA-824), and pyrazinamide (MPa100Z regimen); moxifloxacin, 200 mg pretomanid, and pyrazinamide (MPa200Z regimen); or the current standard care for drug-susceptible pulmonary tuberculosis, isoniazid, rifampicin, PZA, and ethambutol (HRZE regimen). A group of patients with MDR tuberculosis received MPa200Z (DRMPa200Z group). The primary outcome was bactericidal activity measured by the mean daily rate of reduction in M tuberculosis CFUs per mL overnight sputum collected once a week, with joint Bayesian non-linear mixed-effects regression modelling. We also assessed safety and tolerability by monitoring adverse events. This study is registered with ClinicalTrials.gov, number NCT01498419.

FINDINGS:

Between March 24, 2012, and July 26, 2013 we enrolled 207 patients and randomly assigned them to treatment groups; we assigned 60 patients to the MPa100Z regimen, 62 to the MPa200Z regimen, and 59 to the HRZE regimen. We non-randomly assigned 26 patients with drug-resistant tuberculosis to the DRMPa200Z regimen. In patients with drug-susceptible

tuberculosis, the bactericidal activity of MPa200Z (n=54) on days 0-56 (0·155, 95% Bayesian credibility interval 0·133-0·178) was significantly greater than for HRZE (n=54, 0·112, 0·093-0·131). DRMPa200Z (n=9) had bactericidal activity of 0·117 (0·070-0·174). The bactericidal activity on days 7-14 was strongly associated with bactericidal activity on days 7-56. Frequencies of adverse events were similar to standard treatment in all groups. The most common adverse event was hyperuricaemia in 59 (29%) patients (17 [28%] patients in MPa100Z group, 17 [27%] patients in MPa200Z group, 17 [29%] patients. in HRZE group, and 8 [31%] patients in DRMPa200Z group). Other common adverse events were nausea in (14 [23%] patients in MPa100Z group, 8 [13%] patients in MPa200Z group, 7 [12%] patients in HRZE group, and 8 [31%] patients in DRMPa200Z group) and vomiting (7 [12%] patients in MPa100Z group, 7 [11%] patients in MPa200Z group, 7 [12%] patients in HRZE group, and 4 [15%] patients in DRMPa200Z group). No on-treatment electrocardiogram occurrences of corrected QT interval more than 500 ms (an indicator of potential of ventricular tachyarrhythmia) were reported. No phenotypic resistance developed to any of the drugs in the regimen.

INTERPRETATION:

The combination of moxifloxacin, pretomanid, and pyrazinamide, was safe, well tolerated, and showed superior bactericidal activity in drug-susceptible tuberculosis during 8 weeks of treatment. Results were consistent between drug-susceptible and MDR tuberculosis. This new regimen is ready to enter phase 3 trials in patients with drug-susceptible tuberculosis and MDR-tuberculosis, with the goal of shortening and simplifying treatment.

N Engl J Med. 2014 Oct 23;371(17):1599-608. doi: 10.1056/NEJMoa1314210.
Jindani A[1], Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S, Hatherill M, Geldenhuys H, McIlleron HM, Zvada SP, Mungofa S, Shah NA, Zizhou S, Magweta L, Shepherd J, Nyirenda S, van Dijk JH, Clouting HE, Coleman D, Bateson AL, McHugh TD, Butcher PD, Mitchison DA; RIFAQUIN Trial Team.

From St. George's, University of London (A.J., D.A.M., T.S.H., D.C., P.D.B.), Medical Research Council Clinical Trials Unit at University College London (A.J.N., P.P.J.P., H.E.C.), and University College London Centre for Clinical Biology, University College London (A.L.E.B., T.D.M.), London; Aurum Institute (G.J.C., S.C.) and School of Public Health, University of the Witwatersrand (G.J.C.), Johannesburg, and South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine and School of Child and Adolescent Health (M.H., H.G.) and Division of Clinical Pharmacology, Department of Medicine (H.M.M., S.P.Z.), University of Cape Town, Cape Town - all in South Africa; Harare City Health Department, Harare (S.M., N.A.S.S.), and Medical Directorate of Mashonaland East, Marondera (S.Z., L.M.) - both in Zimbabwe; CDC, Gaborone, Botswana (J.S., S.N.); and Macha Research Trust, Macha, Zambia (J.H.D.).

BACKGROUND:

Tuberculosis regimens that are shorter and simpler than the current 6-month daily regimen are needed.

METHODS:

We randomly assigned patients with newly diagnosed, smear-positive, drug-sensitive tuberculosis to one of three regimens: a control regimen that included 2 months of ethambutol,

isoniazid, rifampicin, and pyrazinamide administered daily followed by 4 months of daily isoniazid and rifampicin; a 4-month regimen in which the isoniazid in the control regimen was replaced by moxifloxacin administered daily for 2 months followed by moxifloxacin and 900 mg of rifapentine administered twice weekly for 2 months; or a 6-month regimen in which isoniazid was replaced by daily moxifloxacin for 2 months followed by one weekly dose of both moxifloxacin and 1200 mg of rifapentine for 4 months. Sputum specimens were examined on microscopy and after culture at regular intervals. The primary end point was a composite treatment failure and relapse, with noninferiority based on a margin of 6 percentage points and 90% confidence intervals.

RESULTS:

We enrolled a total of 827 patients from South Africa, Zimbabwe, Botswana, and Zambia; 28% of patients were coinfected with the human immunodefiency virus. In the per-protocol analysis, the proportion of patients with an unfavorable response was 4.9% in the control group, 3.2% in the 6-month group (adjusted difference from control, -1.8 percentage points; 90% confidence interval [CI], -6.1 to 2.4), and 18.2% in the 4-month group (adjusted difference from control, 13.6 percentage points; 90% CI, 8.1 to 19.1). In the modified intention-to-treat analysis these proportions were 14.4% in the control group, 13.7% in the 6-month group (adjusted difference from control, 0.4 percentage points; 90% CI, -4.7 to 5.6), and 26.9% in the 4-month group (adjusted difference from control, 13.1 percentage points; 90% CI, 6.8 to 19.4).

CONCLUSIONS:

The 6-month regimen that included weekly administration of high-dose rifapentine and moxifloxacin was as effective as the control regimen. The 4-month regimen was not noninferior to the control regimen.

Antimicrob Agents Chemother. 2014 Oct;58(10):6242-50. doi: 10.1128/AAC.03073-14. Epub 2014 Aug 11.

Pharmacokinetics of para-aminosalicylic acid in HIV-uninfected and HIV-coinfected tuberculosis patients receiving antiretroviral therapy, managed for multidrug-resistant and extensively drug-resistant tuberculosis.

de Kock L[1], Sy SK[2], Rosenkranz B[3], Diacon AH[4], Prescott K[1], Hernandez KR[2], Yu M[2], Derendorf H[2], Donald PR[5].

Division of Clinical Pharmacology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.; Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, Florida, USA.; Division of Clinical Pharmacology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; Department of Biomedical Science, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.; Pediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.

Abstract

The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Mycobacterium tuberculosis prompted the reintroduction of para-aminosalicylic acid (PAS) to protect companion anti-tuberculosis drugs from additional acquired resistance. In sub-Saharan Africa, MDR/XDR tuberculosis with HIV coinfection is common, and concurrent treatment of

HIV infection and MDR/XDR tuberculosis is required. Out of necessity, patients receive multiple drugs, and PAS therapy is frequent; however, neither potential drug interactions nor the effects of HIV infection are known. Potential drug-drug interaction with PAS and the effect of HIV infection was examined in 73 pulmonary tuberculosis patients; 22 (30.1%) were HIV coinfected. Forty-one pulmonary MDR or XDR tuberculosis patients received 4 g PAS twice daily, and in a second crossover study, another 32 patients were randomized, receiving 4 g PAS twice daily or 8 g PAS once daily. A PAS population pharmacokinetic model in two dosing regimens was developed; potential covariates affecting its pharmacokinetics were examined, and Monte Carlo simulations were conducted evaluating the pharmacokinetic-pharmacodynamic index. The probability of target attainment (PTA) to maintain PAS levels above MIC during the dosing interval was estimated by simulation of once-, twice-, and thrice-daily dosing regimens not exceeding 12 g daily. Concurrent efavirenz (EFV) medication resulted in a 52% increase in PAS clearance and a corresponding >30% reduction in mean PAS area under the concentration curve in 19 of 22 HIV-M. Tuberculosis-coinfected patients. Current practice recommends maintenance of PAS concentrations at ≥1 μg/ml (the MIC of M. tuberculosis), but the model predicts that at only a minimum dose of 4 g twice daily can this PTA be achieved in at least 90% of the population, whether or not EFV is concomitantly administered. Once-daily dosing of 12 g PAS will not provide PAS concentrations exceeding the MIC over the entire dosing interval if coadministered with EFV, while 4 g twice daily ensures concentrations exceeding MIC over the entire dosing interval, even in HIV-infected patients who received EFV.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4187930/pdf/zac6242.pdf

Am J Clin Nutr. 2014 Nov;100(5):1287-97. doi: 10.3945/ajcn.113.082255. Epub 2014 Sep 10.

Effect of micronutrient supplementation on treatment outcomes in children with intrathoracic tuberculosis: a randomized controlled trial.

Lodha R[1], Mukherjee A[1], Singh V[1], Singh S[1], Friis H[1], Faurholt-Jepsen D[1], Bhatnagar S[1], Saini S[1], Kabra SK[1], Grewal HM[1]; Delhi Pediatric TB Study Group.

From the Department of Pediatrics (RL, AM, SB, S Saini, and SKK) and Division of Clinical Microbiology & Molecular Medicine, Laboratory Medicine (S Singh), All India Institute of Medical Sciences, New Delhi, India; the Department of Pediatrics, Kalawati Saran Children Hospital, New Delhi, India (VS); the Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark (HF and DF-J); and the Department of Clinical Science, Infection, University of Bergen, Bergen, Norway (HMSG).

BACKGROUND:

Micronutrients play an important role in immune function. To our knowledge, there have been no comprehensive studies on the role of micronutrient supplementation in children with tuberculosis.

OBJECTIVE:

We assessed the effect of micronutrient supplementation in children treated with antituberculosis therapy (ATT).

DESIGN:

A randomized, double-blind, placebo-controlled trial that used a 2 × 2 factorial design was undertaken at 2 teaching hospitals in Delhi. Children with newly diagnosed intrathoracic tuberculosis were enrolled, and they received ATT together with daily supplementation for 6 mo with either zinc alone, micronutrients without zinc, micronutrients in combination with zinc, or a placebo. Main outcomes were weight gain and an improvement in a chest X-ray (CXR) lesion assessed at 6 mo of treatment.

RESULTS:

A total of 403 children were enrolled and randomly assigned. A microbiological diagnosis of tuberculosis was confirmed in 179 children (44.4%). The median (95% CI) increase in weight-for-age z score at 6 mo was not significantly different between subjects who received micronutrients [0.75 (0.66, 0.84)] and those who did not receive micronutrients [0.76 (0.67, 0.85)] and between subjects who received zinc [0.76 (0.68, 0.85)] and those who did not receive zinc [0.75 (0.66, 0.83)]. An improvement in CXR was observed in 285 children, but there was no difference between those receiving zinc and no zinc or between those receiving micronutrients and no micronutrients after 6 mo of ATT. However, children who received micronutrients had a faster gain in height over 6 mo than did those who did not receive micronutrients (height-for-age z score $\Delta = 0.08$; $P = 0.014$).

CONCLUSIONS:

Micronutrient supplementation did not modify the weight gain or clearance of lesions on CXR in children with intrathoracic tuberculosis. However, micronutrient supplementation during treatment may improve height gain in children with intrathoracic tuberculosis.

Indian J Med Res. 2014 Oct;140(4):531-7.

Vitamin D levels in Indian children with intrathoracic tuberculosis.

Khandelwal D, Gupta N, Mukherjee A, Lodha R[1], Singh V, Grewal HM, Bhatnagar S, Singh S, Kabra SK; Delhi Pediatric TB Study Group.

Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

BACKGROUND & OBJECTIVES:

Deficiency of vitamin D, an immunomodulator agent, is associated with increased susceptibility to tuberculosis in adults, but only limited studies are available in the paediatric age group, especially regarding association of vitamin D with type and outcome of tuberculosis. We conducted this study to determine the baseline 25-hydroxy vitamin D levels in children suffering from intrathoracic tuberculosis and its association with type and outcome of tuberculosis.

METHODS:

Children with intrathoracic tuberculosis, diagnosed on the basis of clinico-radiological criteria, were enrolled as part of a randomized controlled trial on micronutrient supplementation in paediatric tuberculosis patients. Levels of 25-hydroxy vitamin D were measured in serum samples collected prior to starting antitubercular therapy by chemiluminescent immunoassay technology.

RESULTS:

Two hundred sixty six children (mean age of 106.9 ± 43.7 months; 57.1% girls) were enrolled. Chest X-ray was suggestive of primary pulmonary complex, progressive disease and pleural effusion in 81 (30.5%), 149 (56%) and 36 (13.5%) subjects, respectively. Median serum 25-hydroxy vitamin D level was 8 ng/ml (IQR 5, 12). One hundred and eighty six (69.9%) children were vitamin D deficient (serum 25-hydroxy vitamin D <12 ng/ml), 55 (20.7%) were insufficient (12 to <20 ng/ml) and 25 (9.4%) were vitamin D sufficient (≥ 20 ng/ml). Levels of 25-hydroxy vitamin D were similar in all three types of intrathoracic tuberculosis, and in microbiologically confirmed and probable cases. Levels of 25-hydroxy vitamin D did not significantly affect outcome of the disease. Children who were deficient or insufficient were less likely to convert (become smear/culture negative) at two months as compared to those who were 25-hydroxy vitamin D sufficient (p <0.05).

INTERPRETATION & CONCLUSIONS:

Majority of Indian children with newly diagnosed intrathoracic tuberculosis were deficient in vitamin D. Type of disease or outcome was not affected by 25-hydroxy vitamin D levels in these children. However, children who did not demonstrate sputum conversion after intensive phase of antitubercular therapy had lower baseline 25-hydroxy vitamin D levels as compared to those who did.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4277140/

BMC Med. 2014 Jul 17;12:120. doi: 10.1186/s12916-014-0120-7.

The association between the ratio of monocytes:lymphocytes at age 3 months and risk of tuberculosis (TB) in the first two years of life.

Naranbhai V, Kim S, Fletcher H, Cotton MF, Violari A, Mitchell C, Nachman S, McSherry G, McShane H, Hill AV, Madhi SA.

BACKGROUND:

Recent transcriptomic studies revived a hypothesis suggested by historical studies in rabbits that the ratio of peripheral blood monocytes to lymphocytes (ML) is associated with risk of tuberculosis (TB) disease. Recent data confirmed the hypothesis in cattle and in adults infected with HIV.

METHODS:

We tested this hypothesis in 1,336 infants (540 HIV-infected, 796 HIV-exposed, uninfected (HEU)) prospectively followed in a randomized controlled trial of isoniazid prophylaxis in Southern Africa, the IMPAACT P1041 study. We modeled the relationship between ML ratio at enrollment (91 to 120 days after birth) and TB disease or death in HIV-infected children and latent Mycobacterium tuberculosis (MTB) infection, TB disease or death in HEU children within 96 weeks (with 12 week window) of randomization. Infants were followed-up prospectively and routinely assessed for MTB exposure and outcomes. Cox proportional hazards models allowing for non-linear associations were used; in all cases linear models were the most parsimonious.

RESULTS:

Increasing ML ratio at baseline was significantly associated with TB disease/death within two years (adjusted hazard ratio (HR) 1.17 per unit increase in ML ratio; 95% confidence interval (CI) 1.01 to 1.34; P = 0.03). Neither monocyte count nor lymphocyte counts alone were associated with TB disease. The association was not statistically dissimilar between HIV infected and HEU children. Baseline ML ratio was associated with composite endpoints of TB disease and death and/or TB infection. It was strongest when restricted to probable and definite TB disease (HR 1.50; 95% CI 1.19 to 1.89; P = 0.006). Therefore, per 0.1 unit increase in the ML ratio at three to four months of age, the hazard of probable or definite TB disease before two years was increased by roughly 4% (95% CI 1.7% to 6.6%).

CONCLUSION:

Elevated ML ratio at three- to four-months old is associated with increased hazards of TB disease before two years among children in Southern Africa. While significant, the modest effect size suggests that the ML ratio plays a modest role in predicting TB disease-free survival; its utility may, therefore, be limited to combination with existing tools to stratify TB risk, or to inform underlying pathophysiologic determinants of TB disease.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223414/

Cochrane Database Syst Rev. 2014 Nov 18;11:CD006594. doi: 10.1002/14651858.CD006594.pub3.

Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment.

Liu Q[1], Abba K, Alejandria MM, Sinclair D, Balanag VM, Lansang MA.

China Effective Health Care Network, School of Public Health & Management, Chongqing Medical University, Chongqing, China,

BACKGROUND:

People with active tuberculosis (TB) require six months of treatment. Some people find it difficult to complete treatment, and there are several approaches to help ensure completion. One such system relies on reminders, where the health system prompts patients to attend for appointments on time, or re-engages people who have missed or defaulted on a scheduled appointment.

OBJECTIVES:

To assess the effects of reminder systems on improving attendance at TB diagnosis, prophylaxis, and treatment clinic appointments, and their effects on TB treatment outcomes.

SEARCH METHODS:

We searched the Cochrane Infectious Diseases Group Specialized Register, Cochrane Effective Practice and Organization of Care Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, CINAHL, SCI-EXPANDED, SSCI, mRCT, and the Indian Journal of Tuberculosis without language restriction up to 29 August 2014. We also checked reference lists and contacted researchers working in the field.

SELECTION CRITERIA:

Randomized controlled trials (RCTs), including cluster RCTs and quasi-RCTs, and controlled before-and-after studies comparing reminder systems with no reminders or an alternative reminder system for people with scheduled appointments for TB diagnosis, prophylaxis, or treatment.

DATA COLLECTION AND ANALYSIS:

Two review authors independently extracted data and assessed the risk of bias in the included trials. We compared the effects of interventions by using risk ratios (RR) and presented RRs with 95% confidence intervals (CIs). Also we assessed the quality of evidence using the GRADE approach.

MAIN RESULTS:

Nine trials, including 4654 participants, met our inclusion criteria. Five trials evaluated appointment reminders for people on treatment for active TB, two for people on prophylaxis for latent TB, and four for people undergoing TB screening using skin tests. We classified the interventions into 'pre-appointment' reminders (telephone calls or letters prior to a scheduled appointment) or 'default' reminders (telephone calls, letters, or home visits to people who had missed an appointment).For people being treated for active TB, clinic attendance and TB treatment completion were higher in people receiving pre-appointment reminder phone-calls (clinic attendance: 66% versus 50%; RR 1.32, 95% CI 1.10 to 1.59, one trial (USA), 615 participants, low quality evidence; TB treatment completion: 100% versus 88%; RR 1.14, 95% CI 1.02 to 1.27, one trial (Thailand), 92 participants, low quality evidence). Clinic attendance and TB treatment completion were also higher with default reminders (letters or home visits) (clinic attendance: 52% versus 10%; RR 5.04, 95% CI 1.61 to 15.78, one trial (India), 52 participants, low quality evidence; treatment completion: RR 1.17, 95% CI 1.11 to 1.24, two trials (Iraq and India), 680 participants, moderate quality evidence).For people on TB prophylaxis, clinic attendance was higher with a policy of pre-appointment phone-calls (63% versus 48%; RR 1.30, 95% CI 1.07 to 1.59, one trial (USA), 536 participants); and attendance at the final clinic was higher with regular three-monthly phone-calls or nurse visits (93% versus 65%, one trial (Spain), 318 participants).For people undergoing screening for TB, three trials of pre-appointment phone-calls found little or no effect on the proportion of people returning to clinic for the result of their skin test (three trials, 1189 participants, low quality evidence), and two trials found little or no effect with take home reminder cards (two trials, 711 participants). All four trials were conducted among healthy volunteers in the USA.

AUTHORS' CONCLUSIONS:

Policies of sending reminders to people pre-appointment, and contacting people who miss appointments, seem sensible additions to any TB programme, and the limited evidence available suggests they have small but potentially important benefits. Future studies of modern technologies such as short message service (SMS) reminders would be useful, particularly in low-resource settings.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4448217/pdf/CD006594-0001.pdf

Urinary tract infection

Pediatr Nephrol. 2015 Mar;30(3):479-86. doi: 10.1007/s00467-014-2943-z. Epub 2014 Aug 31.

Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial.

Hari P[1], Hari S, Sinha A, Kumar R, Kapil A, Pandey RM, Bagga A.
Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi,

BACKGROUND:

The benefits of long-term low-dose antibiotics in preventing urinary tract infection (UTI) and renal damage in children with primary vesicoureteric reflux (VUR) are unclear.

METHODS:

Children aged between 1 and 12 years with VUR grade I-IV and a microbiologically proven UTI were randomized into two groups to receive either antibiotic prophylaxis [2 mg/kg trimethoprim + sulfamethoxazole (TMP-SMX)] daily or placebo, respectively, for 12 months. Primary outcome was microbiologically confirmed symptomatic UTI. Intention-to-treat analysis using time-to-event data was performed.

RESULTS:

A total of 93 children (66.7 % boys) with a median age of 4.6 years were enrolled in this study; VUR grade III-IV was present in 73.1 % of these children. At least one symptomatic UTI occurred in ten (21.3 %) patients receiving antibiotic prophylaxis and in three (6.5 %) patients receiving placebo [hazard ratio in antibiotic group 3.9; 95 % confidence interval (CI) 1- 14; log rank test P = 0.02). Compared to the group receiving placebo, the antibiotic group had a 14.8 % increased risk for developing UTI (95 % CI 1-28; P = 0.03). Of the total number of episodes of UTI, 58.3 % of those in the antibiotic group were caused by TMP-SMX-resistant bacteria compared to 20 % in the placebo group (P = 0.15). A renal scan at 12 months revealed that six of 37 (16.2 %) patients in the antibiotic group and seven of 43 (16.3 %) patients in the placebo group had new or worsening of pre-existing scar.

CONCLUSIONS:

Long-term antibiotic prophylaxis with TMP-SMX is associated with increased risk of symptomatic UTI compared to placebo in children with grade I-IV VUR.

Vaccines and immunization

(see also deworming)

Am J Trop Med Hyg. 2015 Apr;92(4):744-51. doi: 10.4269/ajtmh.14-0518. Epub 2015 Feb 23.

The "Performance of Rotavirus and Oral Polio Vaccines in Developing Countries" (PROVIDE) study: description of methods of an interventional study designed to explore complex biologic problems.

Kirkpatrick BD[1], Colgate ER[1], Mychaleckyj JC[2], Haque R[2], Dickson DM[2], Carmolli MP[2], Nayak U[2], Taniuchi M[2], Naylor C[2], Qadri F[2], Ma JZ[2], Alam M[2], Walsh MC[2], Diehl SA[2]; PROVIDE Study Teams, Petri WA Jr[2].

Department of Medicine and Vaccine Testing Center, The University of Vermont College of Medicine, Burlington, Vermont; Departments of Medicine, The University of Virginia, Charlottesville, Virginia; The icddr,b, Dhaka, Bangladesh.; Department of Medicine and Vaccine Testing Center, The University of Vermont College of Medicine, Burlington, Vermont; Departments of Medicine, The University of Virginia, Charlottesville, Virginia; The icddr,b, Dhaka, Bangladesh.

Abstract

Oral vaccines appear less effective in children in the developing world. Proposed biologic reasons include concurrent enteric infections, malnutrition, breast milk interference, and environmental enteropathy (EE). Rigorous study design and careful data management are essential to begin to understand this complex problem while assuring research subject safety. Herein, we describe the methodology and lessons learned in the PROVIDE study (Dhaka, Bangladesh). A randomized clinical trial platform evaluated the efficacy of delayed-dose oral rotavirus vaccine as well as the benefit of an injectable polio vaccine replacing one dose of oral polio vaccine. This rigorous infrastructure supported the additional examination of hypotheses of vaccine underperformance. Primary and secondary efficacy and immunogenicity measures for rotavirus and polio vaccines were measured, as well as the impact of EE and additional exploratory variables. Methods for the enrollment and 2-year follow-up of a 700 child birth cohort are described, including core laboratory, safety, regulatory, and data management practices. Intense efforts to standardize clinical, laboratory, and data management procedures in a developing world setting provide clinical trials rigor to all outcomes. Although this study infrastructure requires extensive time and effort, it allows optimized safety and confidence in the validity of data gathered in complex, developing country settings.

Cholera vaccine

Am J Trop Med Hyg. 2015 Jun 15. pii: 14-0683. [Epub ahead of print]

A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia.

Desai SN[1], Akalu Z[2], Teshome S[2], Teferi M[2], Yamuah L[2], Kim DR[2], Yang JS[2], Hussein J[2], Park JY[2], Jang MS[2], Mesganaw C[2], Taye H[2], Beyene D[2], Bedru A[2], Singh AP[2], Wierzba TF[2], Aseffa A[2].

International Vaccine Institute, Seoul, Korea; Armauer Hansen Research Institute, Addis Ababa, Ethiopia.

Abstract

Killed whole-cell oral cholera vaccine (OCV) has been a key component of a comprehensive package including water and sanitation measures for recent cholera epidemics. The vaccine, given in a two-dose regimen, has been evaluated in a large number of human volunteers in India, Vietnam, and Bangladesh, where it has demonstrated safety, immunogenicity, and clinical efficacy. We conducted a double-blind randomized placebo-controlled trial in Ethiopia, where

we evaluated the safety and immunogenicity of the vaccine in 216 healthy adults and children. OCV was found to be safe and elicited a robust immunological response against Vibrio cholerae O1, with 81% adults and 77% children demonstrating seroconversion 14 days after the second dose of vaccine. This is the first study to evaluate safety and immunogenicity of the vaccine in a population outside Asia using a placebo-controlled, double-blind, randomized study design.

PLoS Negl Trop Dis. 2015 Mar 12;9(3):e0003574. doi: 10.1371/journal.pntd.0003574. eCollection 2015.

Flexibility of oral cholera vaccine dosing-a randomized controlled trial measuring immune responses following alternative vaccination schedules in a cholera hyper-endemic zone.

Kanungo S[1], Desai SN[2], Nandy RK[3], Bhattacharya MK[4], Kim DR[2], Sinha A[3], Mahapatra T[1], Yang JS[5], Lopez AL[6], Manna B[7], Bannerjee B[7], Ali M[8], Dhingra MS[9], Chandra AM[10], Clemens JD[11], Sur D[12], Wierzba TF[2].

Division of Epidemiology, National Institute of Cholera and Enteric Diseases, Kolkata, India.; Development and Delivery Unit, International Vaccine Institute, Seoul, Republic of Korea.; Division of Bacteriology, National Institute of Cholera and Enteric Diseases, Kolkata, India.; Division of Clinical Medicine, National Institute of Cholera and Enteric Diseases, Kolkata, India.; Laboratory Science Division, International Vaccine Institute, Seoul, Republic of Korea.; University of the Philippines Manila, National Institutes of Health, Manila, Philippines.; Division of Data Management, National Institute of Cholera and Enteric Diseases, Kolkata, India.; Development and Delivery Unit, International Vaccine Institute, Seoul, Republic of Korea; Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America.; Clinical Research and Development, Shantha Biotechnics Private Limited, Hyderabad, India.; Department of Physiology, Calcutta University, Kolkata.; Office of the Executive Director, International Centre for Diarrheal Disease Research, Bangladesh; Department of Epidemiology, University of California Los Angeles Fielding School of Public Health, Los Angeles, United States of America.;

Division of Epidemiology, National Institute of Cholera and Enteric Diseases, Kolkata, India; Office of the Scientific Director, PATH India Office, New Delhi, India.

BACKGROUND:

A bivalent killed whole cell oral cholera vaccine has been found to be safe and efficacious for five years in the cholera endemic setting of Kolkata, India, when given in a two dose schedule, two weeks apart. A randomized controlled trial revealed that the immune response was not significantly increased following the second dose compared to that after the first dose. We aimed to evaluate the impact of an extended four week dosing schedule on vibriocidal response.

METHODOLOGY/PRINCIPAL FINDINGS:

In this double blind randomized controlled non-inferiority trial, 356 Indian, non-pregnant residents aged 1 year or older were randomized to receive two doses of oral cholera vaccine at 14 and 28 day intervals. We compared vibriocidal immune responses between these schedules. Among adults, no significant differences were noted when comparing the rates of seroconversion for V. cholerae O1 Inaba following two dose regimens administered at a 14 day interval (55%) vs the 28 day interval (58%). Similarly, no differences in seroconversion were demonstrated in children comparing the 14 (80%) and 28 day intervals (77%). Following 14 and

28 day dosing intervals, vibriocidal response rates against V. cholerae O1 Ogawa were 45% and 49% in adults and 73% and 72% in children respectively. Responses were lower for V. cholerae O139, but similar between dosing schedules for adults (20%, 20%) and children (28%, 20%).

CONCLUSIONS/SIGNIFICANCE:

Comparable immune responses and safety profiles between the two dosing schedules support the option for increased flexibility of current OCV dosing. Further operational research using a longer dosing regimen will provide answers to improve implementation and delivery of cholera vaccination in endemic and epidemic outbreak scenarios.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4357440/pdf/pntd.0003574.pdf

Dengue vaccine

Lancet. 2014 Oct 11;384(9951):1358-65. doi: 10.1016/S0140-6736(14)61060-6. Epub 2014 Jul 10.

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial.

Capeding MR[1], Tran NH[2], Hadinegoro SR[3], Ismail HI[4], Chotpitayasunondh T[5], Chua MN[6], Luong CQ[2], Rusmil K[7], Wirawan DN[8], Nallusamy R[9], Pitisuttithum P[10], Thisyakorn U[11], Yoon IK[12], van der Vliet D[13], Langevin E[14], Laot T[15], Hutagalung Y[16], Frago C[16], Boaz M[17], Wartel TA[16], Tornieporth NG[14], Saville M[18], Bouckenooghe A[16]; CYD14 Study Group.

Research Institute for Tropical Medicine, Alabang, Muntinlupa City, Philippines.; Pasteur Institute Ho Chi Minh City, Ho Chi Minh City, Vietnam.; Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.; Pediatric Institute, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia.; Queen Sirikit National Institute of Child Health, Bangkok, Thailand.; Chong Hua Hospital, Cebu City Guadalupe Health Center Annex, Guadalupe, Cebu City, Philippines; Child Health Department, Hasan Sadikin Hospital-Faculty of Medicine, Padjadjaran University, Bandung, Indonesia.; Department of Preventive Medicine, School of Medicine, Udayana University, Denpasar, Bali, Indonesia; Department of Paediatrics, Penang Hospital, Penang, Malaysia.;Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University, Ratchathewi, Bangkok, Thailand.; Dengue Project Banpong-Photharam, Faculty of Tropical Medicine, Mahidol University, Ratchathewi, Bangkok, Thailand.; Department of Virology, US Army Medical Component-Armed Forces Research Institute of Medical Sciences (USAMC-AFRIMS), US Army Medical Component, Bangkok, Thailand.;Sanofi Pasteur, Marcy-l'Étoile, France. ; Sanofi Pasteur, Marcy-l'Étoile, France; Sanofi Pasteur, Makati City, Philippines.; Sanofi Pasteur, Singapore, Singapore.; Sanofi Pasteur, Swiftwater, PA, USA; Sanofi Pasteur, Lyon, France.

BACKGROUND:

An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

METHODS:

We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2-14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol.

FINDINGS:

We randomly assigned 10,275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8-66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

INTERPRETATION:

Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2-14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.

http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(14)61060-6.pdf

HIV vaccine

Vaccine. 2014 Oct 7;32(44):5801-8. doi: 10.1016/j.vaccine.2014.08.034. Epub 2014 Aug 27.

PedVacc 002: a phase I/II randomized clinical trial of MVA.HIVA vaccine administered to infants born to human immunodeficiency virus type 1-positive mothers in Nairobi.

Njuguna IN[1], Ambler G[2], Reilly M[3], Ondondo B[4], Kanyugo M[1], Lohman-Payne B[1], Gichuhi C[5], Borthwick N[4], Black A[4], Mehedi SR[6], Sun J[3], Maleche-Obimbo E[1], Chohan B[1], John-Stewart GC[7], Jaoko W[8], Hanke T[9].

Department of Pediatrics and Child Health, University of Nairobi; Department of Global Health, University of Washington, Seattle, ; Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden.; The Jenner Institute, University of Oxford, Oxford

OX3 7DQ, UK.; Department of Clinical Medicine and Therapeutics, University of NairobiNairobi, Kenya.; Statistics and Data Management Department, Medical Research Council Unit, Fajara, The Gambia.; Departments of Pediatrics, Medicine, Epidemiology, and Global Health, University of Washington, Seattle, ; KAVI-Institute of Clinical Research, University of Nairobi, Nairobi, Kenya.; The Jenner Institute, University of Oxford, Oxford OX3 7DQ, UK; The Weatherall Institute of Molecular Medicine, University of Oxford,UK.

BACKGROUND:

A safe, effective vaccine for breastfeeding infants born to HIV-1-positive mothers could complement antiretroviral therapy (ART) for prevention of mother-to-child transmission of HIV-1. To date, only a few HIV-1 vaccine candidates have been tested in infants.

TRIAL DESIGN:

A phase I/II randomized controlled trial PedVacc 002 was conducted to determine the safety and immunogenicity of a single, low dose of MVA.HIVA vaccine delivered intramuscularly to healthy 20-week-old infants born to HIV-1-positive mothers in Nairobi, Kenya.

METHODS:

Pregnant HIV-1-positive women in the 2nd/3rd trimester of gestation were enrolled, provided with ART and self-selected their infant-feeding modality. Infants received nevirapine and cotrimoxazole prophylaxis. At 20 weeks of age, eligible HIV-1-negative infants were randomized to vaccine versus no-treatment arms and followed to 48 weeks of age for assessments of vaccine safety, HIV-1-specific T-cell responses and antibodies to routine childhood vaccines.

RESULTS:

Between February and November 2010, 182 mothers were screened, 104 were eligible and followed on ART during pregnancy/postpartum, of whom 73 had eligible infants at 20 weeks postpartum. Thirty-six infants were randomized to vaccine and 37 to no treatment. Eighty-four percent of infants breastfed, and retention at 48 weeks was 99%. Adverse events were rare and similar between the two arms. HIV-1-specific T-cell frequencies in interferon-γ ELISPOT assay were transiently higher in the MVA.HIVA arm (p=0.002), but not above the threshold for a positive assay. Protective antibody levels were adequate and similar between arms for all routine childhood vaccines except HBV, where 71% of MVA.HIVA subjects compared to 92% of control subjects were protected (p=0.05).

CONCLUSIONS:

This trial tested for the first time an MVA-vectored candidate HIV-1 vaccine in HIV-1-exposed infants in Africa, demonstrating trial feasibility and vaccine safety, low immunogenicity, and compatibility with routine childhood vaccinations. These results are reassuring for use of the MVA vector in more potent prime-boost regimens.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4414927/

HPV vaccine

Pediatr Infect Dis J. 2014 Dec;33(12):1255-61. doi: 10.1097/INF.0000000000000460.

Long-term immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in 10- to 14-year-old girls: open 6-year follow-up of an initial observer-blinded, randomized trial.

Schwarz TF[1], Huang LM, Lin TY, Wittermann C, Panzer F, Valencia A, Suryakiran PV, Lin L, Descamps D.

From the *Central Laboratory and Vaccination Centre, Stiftung Juliusspital Wuerzburg, Wuerzburg, Germany; †National Taiwan University Hospital, Taipei, Taiwan; ‡Chang Gung Memorial Hospital, Chang Gung Children's Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan; §Praxis für Kinder- und Jugendmedizin, Weilheim i.OB, Germany; ¶Gemeinschaftspraxis für Kinder- und Jugendmedizin, Mannheim, Germany; ||Fundación Santa Fe de Bogotá, Bogota, Colombia; **GlaxoSmithKline Vaccines, Bangalore, India; ††XPE Pharma and Science, Wavre, Belgium on behalf of GlaxoSmithKline Vaccines; and §§GlaxoSmithKline Vaccines, Wavre, Belgium.

BACKGROUND:

Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine were evaluated up to 6 years postvaccination (month 72) in preteen/adolescent girls.

METHODS:

Participants, who had received 3 HPV-16/18 AS04-adjuvanted vaccine doses at 10-14 years of age in an initial controlled, observer-blinded, randomized study (NCT00196924) and participated in the open 3-year follow-up (NCT00316706), were invited to continue the follow-up for up to 10 years postvaccination (NCT00877877). Anti-HPV-16 and -18 antibody titers were measured by enzyme-linked immunosorbent assays at yearly visits and were used to fit the modified power-law and piecewise models, predicting long-term immunogenicity. Serious adverse events (SAEs) and pregnancy information were recorded.

RESULTS:

In the according-to-protocol immunogenicity cohort, all participants (N = 505) with data available remained seropositive for anti-HPV-16 and -18 antibodies at month 72. In initially seronegative participants, anti-HPV-16 and -18 antibody geometric mean titers were 65.8- and 33.0-fold higher than those associated with natural infection (NCT00122681) and 5.0- and 2.5-fold higher than those measured at month 69-74 in a study demonstrating vaccine efficacy in women aged 15-25 years (NCT00120848). Exploratory antibody modeling, based on the 6-year data, predicted that vaccine-induced population anti-HPV-16 and -18 antibody geometric mean titers would remain above those associated with natural infection for at least 20 years postvaccination. The HPV-16/18 AS04-adjuvanted vaccine safety profile was clinically acceptable.

CONCLUSIONS:

In preteen/adolescent girls, the HPV-16/18 AS04-adjuvanted vaccine induced high anti-HPV-16 and -18 antibody levels up to 6 years postvaccination, which were predicted to remain above those induced by natural infection for at least 20 years.

Influenza vaccine

N Engl J Med. 2014 Sep 4;371(10):918-31. doi: 10.1056/NEJMoa1401480.

Influenza vaccination of pregnant women and protection of their infants.

Madhi SA[1], Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, Adrian PV, van Niekerk N, Treurnicht F, Ortiz JR, Venter M, Violari A, Neuzil KM, Simões EA, Klugman KP, Nunes MC; Maternal Flu Trial (Matflu) Team.

From the Medical Research Council, Respiratory and Meningeal Pathogens Research Unit (S.A.M., C.L.C., L.K., A.H., S.J., P.V.A., N.N., K.P.K., M.C.N.), the Department of Science and Technology-National Research Foundation, Vaccine-Preventable Diseases (S.A.M., C.L.C., L.K., A.H., S.J., P.V.A., N.N., M.C.N.), and the Perinatal HIV Research Unit (A.V.), University of the Witwatersrand, the National Institute for Communicable Diseases, the National Health Laboratory Service, Centre for Vaccines and Immunology (S.A.M., F.T., M.V.), Johannesburg, and the Department of Medical Virology, University of Pretoria, Pretoria (M.V.) - all in South Africa; the School of Medicine and Children's Hospital, University of Colorado (A.W.), the Department of Pediatrics, Medicine and Pathology, University of Colorado School of Medicine (E.A.F.S.), and the Center for Global Health, Department of Epidemiology, Colorado School of Public Health (E.A.F.S.) - all in Aurora, Colorado; the Department of Medicine and Department of Global Health, University of Washington (J.R.O.), and the Vaccine Access and Delivery Global Program, PATH (J.R.O., K.M.N.) - both in Seattle; and the Hubert Department of Global Health, Rollins School of Public Health, and the Division of Infectious Diseases, School of Medicine, Emory University, Atlanta (K.P.K.).

BACKGROUND:

There are limited data on the efficacy of vaccination against confirmed influenza in pregnant women with and those without human immunodeficiency virus (HIV) infection and protection of their infants.

METHODS:

We conducted two double-blind, randomized, placebo-controlled trials of trivalent inactivated influenza vaccine (IIV3) in South Africa during 2011 in pregnant women infected with HIV and during 2011 and 2012 in pregnant women who were not infected. The immunogenicity, safety, and efficacy of IIV3 in pregnant women and their infants were evaluated until 24 weeks after birth. Immune responses were measured with a hemagglutination inhibition (HAI) assay, and influenza was diagnosed by means of reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays of respiratory samples.

RESULTS:

The study cohorts included 2116 pregnant women who were not infected with HIV and 194 pregnant women who were infected with HIV. At 1 month after vaccination, seroconversion rates and the proportion of participants with HAI titers of 1:40 or more were higher among IIV3 recipients than among placebo recipients in both cohorts. Newborns of IIV3 recipients also had higher HAI titers than newborns of placebo recipients. The attack rate for RT-PCR-confirmed influenza among both HIV-uninfected placebo recipients and their infants was 3.6%. The attack rates among HIV-uninfected IIV3 recipients and their infants were 1.8% and 1.9%, respectively, and the respective vaccine-efficacy rates were 50.4% (95% confidence interval [CI], 14.5 to 71.2) and 48.8% (95% CI, 11.6 to 70.4). Among HIV-infected women, the attack rate for placebo recipients was 17.0% and the rate for IIV3 recipients was 7.0%; the vaccine-efficacy rate for these IIV3 recipients was 57.7% (95% CI, 0.2 to 82.1).

CONCLUSIONS:

Influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV.

http://www.nejm.org/doi/pdf/10.1056/NEJMoa1401480

Clin Infect Dis. 2014 Aug 15;59(4):517-24. doi: 10.1093/cid/ciu356. Epub 2014 May 13.

Incidence of influenza virus infections in children in Hong Kong in a 3-year randomized placebo-controlled vaccine study, 2009-2012.

Cowling BJ[1], Perera RA[2], Fang VJ[1], Chan KH[3], Wai W[1], So HC[1], Chu DK[2], Wong JY[1], Shiu EY[1], Ng S[4], Ip DK[5], Peiris JS[2], Leung GM[5].

Division of Epidemiology and Biostatistics, School of Public Health.; Division of Public Health Laboratory Sciences, School of Public Health Centre for Influenza Research.; Department of Microbiology.; Department of Ecology and Evolutionary Biology, Princeton University, New Jersey.; Division of Community Medicine and Public Health Practice, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

BACKGROUND:

School-aged children suffer high rates of influenza virus infections and associated illnesses each year, and are a major source of transmission in the community. However, information on the cumulative incidence of infection in specific epidemics is scarce, and there are limited studies with sufficient follow-up to identify the strength and duration of protection against reinfection.

METHODS:

We randomly allocated children 5-17 years of age to receive trivalent inactivated influenza vaccine (TIV) or placebo from September 2009 through January 2010, and then conducted follow-up for 3 years including regular collection of sera, symptom diaries, and collection of nose and throat swabs during illness episodes in participants or their household members.

RESULTS:

Of 796 children initially randomized, 484 continued to participate for all 3 years. In unvaccinated children, cumulative incidence of infection was estimated to be 59% in the first wave of H1N1pdm09 in 2009-2010, and 7%, 14%, 20%, and 31% in subsequent epidemics of H3N2 (2010), H1N1pdm09 (2011), B (2012), and H3N2 (2012), respectively. Infection with H1N1pdm09 in 2009-2010 and H3N2 in 2010 was associated with protection against infection with subsequent epidemics of the same subtype in 2011 and 2012, respectively, but we found no evidence of heterotypic or heterosubtypic protection against infection.

CONCLUSIONS:

We identified substantial incidence of influenza virus infections in children in Hong Kong in 5 major epidemics over a 3-year period, and evidence of homosubtypic but not heterosubtypic protection following infection.

Vaccine. 2014 Oct 21;32(46):6146-56. doi: 10.1016/j.vaccine.2014.08.068. Epub 2014 Sep 16.

Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children.

Nolan T[1], Bravo L[2], Ceballos A[3], Mitha E[4], Gray G[5], Quiambao B[6], Patel SS[7], Bizjajeva S[7], Bock H[7], Nazaire-Bermal N[7], Forleo-Neto E[7], Cioppa GD[7], Narasimhan V[7].

Melbourne School of Population and Global Health, and the Murdoch Childrens Research Institute, University of Melbourne, Melbourne, Australia. ; Philippine General Hospital, University of the Philippines Manila, Manila, Metro Manila, Philippines.; Instituto Médico Rio Cuarto, Cordoba, Cordoba Province, Argentina.; Newtown Clinical Research Centre, Johannesburg, Gauteng Province, South Africa.; Chris Hani Baragwanath Hospital, University of Witwatersrand, Johannesburg, Gauteng Province, South Africa.; Research Institute for Tropical Medicine, Muntinlupa, Metro Manila, Philippines.

BACKGROUND:

Non-adjuvanted seasonal influenza vaccines show only modest efficacy in young children. This study compared the immunogenicity, reactogenicity and safety of the MF59-adjuvanted trivalent subunit vaccine (aTIV) with two non-adjuvanted trivalent vaccines, TIV-1, the non-adjuvanted version of aTIV, and TIV-2, a split virion vaccine.

METHODS:

6078 children received two doses of aTIV (n=3125), TIV-1 (n=1479), or TIV-2 (n=1474) four weeks apart (Days 1 and 29). Children aged 6 to <36 months and 36 to <72 months received 0.25 mL and 0.50 mL doses, respectively. Immunogenicity was assessed by hemagglutination inhibition (HI) assay (n=2435) on Days 1, 29, 50 and 209. Safety was assessed up to Day 394.

RESULTS:

After the second vaccination (Day 50), the aTIV group showed significantly higher geometric mean HI titers and seroconversion rates than the TIV-1 or TIV-2 groups against all homologous and heterologous strains. The difference was enhanced at HI titers ≥110. aTIV elicited a faster, more persistent antibody response, with significantly higher titers in the aTIV group after one vaccination (Day 29) and after six months (Day 209) than in either TIV group. aTIV was more reactogenic than were TIV-1 and TIV-2 but rates of severe adverse events were very low for all three vaccines.

CONCLUSION:

In infants and young children, the MF59-adjuvanted vaccine induced substantially faster (after one dose), higher, persistent HI titers than the non-adjuvanted vaccines, with consistently higher seroprotection rates at increased threshold HI titers.

Japanese encephalitis virus vaccine

BMC Infect Dis. 2015 Jan 8;15:7. doi: 10.1186/s12879-014-0744-4.

Safety and immunogenicity of a freeze-dried, Vero cell culture-derived, inactivated Japanese encephalitis vaccine (KD-287, ENCEVAC®) versus a mouse brain-derived inactivated Japanese encephalitis vaccine in children: a phase III, multicenter, double-blinded, randomized trial.

Yun KW, Lee HJ, Kang JH, Eun BW, Kim YJ, Kim KH, Kim NH, Hong YJ, Kim DH, Kim HM, Cha SH.

BACKGROUND:

Although mouse brain-derived, inactivated Japanese encephalitis vaccines (JE-MBs) have been successfully used for a long time, potential rare neurological complications have prompted the development of a Vero cell culture-derived inactivated vaccine (JE-VC). In a phase III clinical study, we aimed to compare the safety and immunogenicity of a JE-VC, KD-287 with a JE-MB, JEV-GCC, in children.

METHODS:

In this multicenter, double-blinded, randomized controlled trial, the study population consisted of 205 healthy Korean children aged 12-23 months. Each subject was subcutaneously vaccinated with either KD-287 or JEV-GCC twice at an interval of 2 weeks and then vaccinated once 12 months after the second vaccination. Neutralizing antibodies were measured by the plaque reduction neutralization test using the homologous and heterologous, as a post hoc analysis, challenge virus strains.

RESULTS:

The three-dose regimen of KD-287 showed a comparable safety profile with JEV-GCC except higher incidence of fever after the first dose (30.4% and 14.7%, respectively). Most of the fever was mild degree (61.3% and 66.7%, respectively). KD-287 fulfilled the non-inferiority criteria for seroconversion rate (SCR) and geometric mean titer (GMT) of the neutralizing antibody, which were the primary endpoints, at 4 weeks after the third vaccination (95% CI: -1.00, 3.10 for the SCR difference and 10.8, 17.6 for the GMT ratio). The SCRs of KD-287 were all 100% and the GMTs were higher in the KD-287 group than in the JEV-GCC group after the second vaccination and before and after the third vaccination (GMT ratio: 5.59, 20.13, and 13.79, respectively, $p < 0.001$ in all). GMTs were higher in the KD-287 group in the heterologous analysis also (GMT ratio: 4.05, 5.15, and 4.19, respectively, $p < 0.001$ in all).

CONCLUSIONS:

This study suggests that the KD-287, a JE-VC is as safe as and may be more effective than the licensed MB-derived vaccine. KD-287 could thus be useful as a second-generation vaccine and substitute for the current JE-MB vaccine in Korean children.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296691/pdf/12879_2014_Article_744.pdf

Vaccine. 2014 Sep 15;32(41):5363-9. doi: 10.1016/j.vaccine.2014.02.085. Epub 2014 Mar 12.

Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: randomized study in toddlers in Taiwan.

Huang LM[1], Lin TY[2], Chiu CH[3], Chiu NC[4], Chen PY[5], Yeh SJ[6], Boaz M[7], Hutagalung Y[8], Bouckenooghe A[8], Feroldi E[9].

Department of Pediatric, National Taiwan University Hospital, Taipei, Taiwan.; Chang Gung Children's Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan..; Chang Gung Children's Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan.; Mackey Memorial Hospital, Taipei, Taiwan; Taichung Veterans General Hospital, Taichung, Taiwan.; Far Eastern Memorial Hospital, New Taipei City, Taiwan.; Global Clinical Immunology, Sanofi Pasteur, Swiftwater, , USA.; Sanofi Pasteur, Clinical Development, Singapore, Singapore.; Sanofi Pasteur, Clinical Department, Lyon, France.

BACKGROUND:

Japanese encephalitis (JE) is the most important cause of viral encephalitis in Asia.

METHODS:

In this randomized, open-label, multicenter trial in 550 children aged 12 to 18 months in Taiwan, children received one dose of JE-CV and one dose of MMR vaccine. Vaccines were either administered separately 6 weeks apart (Groups 'JE-CV' and 'MMR', named after which vaccine was given first), or concomitantly (Group 'Co-Ad'). JE neutralizing antibody titers were assessed using PRNT50. MMR antibody levels were determined by ELISA.

RESULTS:

All groups had low seroprotection/seropositivity rates (<10%) before vaccination for all antigens. Forty two days after vaccination, on either Study Day 42 or 84, seroconversion rates for all antigens were high in all groups, irrespective of the order of vaccinations. Seroconversion for JE ranged from 96.9% in Group Co-Ad on D42 to 100% in Group MMR. Non-inferiority was demonstrated for all analyses as the lower bound of the 95% CI of the difference in seroconversion rates between groups was above the pre-defined limit of -10.0%. The immune responses remained high for all antigens and well above the level of protection 12 months after vaccination in all groups. There were no safety concerns.

CONCLUSIONS:

JE-CV is safe and induces a strong protective immune response which persists over 1 year when co-administered with MMR vaccine.

Vaccine. 2014 Oct 21;32(46):6061-6. doi: 10.1016/j.vaccine.2014.09.012. Epub 2014 Sep 18.

Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product.

Zaman K[1], Naser AM[2], Power M[3], Yaich M[3], Zhang L[4], Ginsburg AS[3], Luby SP[5], Rahman M[6], Hills S[7], Bhardwaj M[8], Flores J[3].

International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh. ; PATH, Washington, DC, USA.; Chengdu Institute of Biological Products, Co., Ltd., Chengdu, China.; International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh; Stanford University, Palo Alto, CA, USA.; Institute of Epidemiology Disease Control and Research (IEDCR), Dhaka, Bangladesh.; Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.; GVK Biosciences Private Limited, Hyderabad, India.

Abstract

We conducted a four-arm, double-blind, randomized controlled trial among 818 Bangladeshi infants between 10 and 12 months of age to establish equivalence among three lots of live attenuated SA 14-14-2 JE vaccine manufactured by the China National Biotec Group's Chengdu Institute of Biological Products (CDIBP) in a new Good Manufacturing Practice (GMP) facility and to evaluate non-inferiority of the product with a lot of the same vaccine manufactured in CDIBP's original facility. The study took place in two sites in Bangladesh, rural Matlab and Mirpur in urban Dhaka. We collected pre-vaccination (Day 0) and post-vaccination Day 28 (-4 to +14 days) blood samples to assess neutralizing anti-JE virus antibody titers in serum by plaque reduction neutralization tests (PRNT). Seroprotection following vaccination was defined as a PRNT titer ≥1:10 at Day 28 in participants non-immune at baseline. Follow-up for reactogenicity and safety was conducted through home visits at Day 7 and monitoring for serious adverse events through Day 28. Seroprotection rates ranged from 80.2% to 86.3% for all four lots of vaccine. Equivalence of the seroprotection rates between pairs of vaccine lots produced in the new GMP facility was satisfied at the pre-specified 10% margin of the 95% confidence interval (CI) for two of the three pairwise comparisons, but not for the third (-4.3% observed difference with 95% CI of -11.9 to 3.3%). Nevertheless, the aggregate seroprotection rate for all three vaccine lots manufactured in the GMP facility was calculated and found to be within the non-inferiority margin (within 10%) to the vaccine lot produced in the original facility. All four lots of vaccine were safe and well tolerated. These study results should facilitate the use of SA 14-14-2 JE vaccine as a routine component of immunization programs in Asian countries.

Malaria vaccine

Vaccine. 2014 Nov 12;32(48):6556-62. doi: 10.1016/j.vaccine.2014.07.067. Epub 2014 Jul 28.

Immunogenicity and safety of the candidate RTS,S/AS01 vaccine in young Nigerian children: a randomized, double-blind, lot-to-lot consistency trial.

Umeh R[1], Oguche S[2], Oguonu T[1], Pitmang S[2], Shu E[1], Onyia JT[1], Daniyam CA[2], Shwe D[2], Ahmad A[3], Jongert E[3], Catteau G[3], Lievens M[3], Ofori-Anyinam O[3], Leach A[4].

University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Enugu State, Nigeria.; Jos University Teaching Hospital, University of Jos, Jos, Plateau State, Nigeria.; GlaxoSmithKline Vaccines, Rixensart, Belgium.; GlaxoSmithKline Vaccines, Rixensart, Belgium.

BACKGROUND:

For regulatory approval, consistency in manufacturing of vaccine lots is expected to be demonstrated in confirmatory immunogenicity studies using two-sided equivalence trials. This randomized, double-blind study (NCT01323972) assessed consistency of three RTS,S/AS01 malaria vaccine batches formulated from commercial-scale purified antigen bulk lots in terms of anti-CS-responses induced.

METHODS:

Healthy children aged 5-17 months were randomized (1:1:1:1) to receive RTS,S/AS01 at 0-1-2 months from one of three commercial-scale purified antigen bulk lots (1600 litres-fermentation scale; commercial-scale lots), or a comparator vaccine batch made from pilot-scale purified

antigen bulk lot (20 litres-fermentation scale; pilot-scale lot). The co-primary objectives were to first demonstrate consistency of antibody responses against circumsporozoite (CS) protein at one month post-dose 3 for the three commercial-scale lots and second demonstrate non-inferiority of anti-CS antibody responses at one month post-dose 3 for the commercial-scale lots compared to the pilot-scale lot. Safety and reactogenicity were evaluated as secondary endpoints.

RESULTS:

One month post-dose-3, anti-CS antibody geometric mean titres (GMT) for the 3 commercial scale lots were 319.6 EU/ml (95% confidence interval (CI): 268.9-379.8), 241.4 EU/ml (207.6-280.7), and 302.3 EU/ml (259.4-352.3). Consistency for the RTS,S/AS01 commercial-scale lots was demonstrated as the two-sided 95% CI of the anti-CS antibody GMT ratio between each pair of lots was within the range of 0.5-2.0. GMT of the pooled commercial-scale lots (285.8 EU/ml (260.7-313.3)) was non-inferior to the pilot-scale lot (271.7 EU/ml (228.5-323.1)). Each RTS,S/AS01 lot had an acceptable tolerability profile, with infrequent reports of grade 3 solicited symptoms. No safety signals were identified and no serious adverse events were considered related to vaccination.

CONCLUSIONS:

RTS,S/AS01 lots formulated from commercial-scale purified antigen bulk batches induced a consistent anti-CS antibody response, and the anti-CS GMT of pooled commercial-scale lots was non-inferior to that of a lot formulated from a pilot-scale antigen bulk batch.

PLoS Med. 2014 Jul 29;11(7):e1001685. doi: 10.1371/journal.pmed.1001685. eCollection 2014.

Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites.

RTS,S Clinical Trials Partnership.

BACKGROUND:

A malaria vaccine could be an important addition to current control strategies. We report the safety and vaccine efficacy (VE) of the RTS,S/AS01 vaccine during 18 mo following vaccination at 11 African sites with varying malaria transmission.

METHODS AND FINDINGS:

6,537 infants aged 6-12 wk and 8,923 children aged 5-17 mo were randomized to receive three doses of RTS,S/AS01 or comparator vaccine. VE against clinical malaria in children during the 18 mo after vaccine dose 3 (per protocol) was 46% (95% CI 42% to 50%) (range 40% to 77%; VE, $p<0.01$ across all sites). VE during the 20 mo after vaccine dose 1 (intention to treat [ITT]) was 45% (95% CI 41% to 49%). VE against severe malaria, malaria hospitalization, and all-cause hospitalization was 34% (95% CI 15% to 48%), 41% (95% CI 30% to 50%), and 19% (95% CI 11% to 27%), respectively (ITT). VE against clinical malaria in infants was 27% (95% CI 20% to 32%, per protocol; 27% [95% CI 21% to 33%], ITT), with no significant protection against severe malaria, malaria hospitalization, or all-cause hospitalization. Post-vaccination anti-circumsporozoite antibody geometric mean titer varied from 348 to 787 EU/ml across sites in children and from 117 to 335 EU/ml in infants (per protocol). VE waned over time in both age categories (Schoenfeld residuals $p<0.001$). The number of clinical and severe malaria cases

averted per 1,000 children vaccinated ranged across sites from 37 to 2,365 and from -1 to 49, respectively; corresponding ranges among infants were -10 to 1,402 and -13 to 37, respectively (ITT). Meningitis was reported as a serious adverse event in 16/5,949 and 1/2,974 children and in 9/4,358 and 3/2,179 infants in the RTS,S/AS01 and control groups, respectively.

CONCLUSIONS:

RTS,S/AS01 prevented many cases of clinical and severe malaria over the 18 mo after vaccine dose 3, with the highest impact in areas with the greatest malaria incidence. VE was higher in children than in infants, but even at modest levels of VE, the number of malaria cases averted was substantial. RTS,S/AS01 could be an important addition to current malaria control in Africa.

Measles vaccine

N Engl J Med. 2015 Apr 16;372(16):1519-29. doi: 10.1056/NEJMoa1407417.

A randomized, controlled trial of an aerosolized vaccine against measles.

Low N[1], Bavdekar A, Jeyaseelan L, Hirve S, Ramanathan K, Andrews NJ, Shaikh N, Jadi RS, Rajagopal A, Brown KE, Brown D, Fink JB, John O, Scott P, Riveros-Balta AX, Greco M, Dhere R, Kulkarni PS, Henao Restrepo AM.

From the Institute of Social and Preventive Medicine, University of Bern, Bern (N.L., P.S.), and the World Health Organization (WHO), Geneva (A.X.R.-B., A.M.H.R.) - both in Switzerland; the Department of Pediatrics, King Edward Memorial Hospital Research Centre (A.B.), the National Institute of Virology (N.S., R.S.J.), the Serum Institute of India (R.D., P.S.K.), and Shirdi Sai Baba Hospital (S.H.), Pune, the Department of Biostatistics, Christian Medical College, Vellore (L.J., K.R., A.R.), and the WHO Regional Office for South-East Asia, New Delhi (O.J.) - all in India; the Statistics Unit (N.J.A.) and Virus Reference Department (K.E.B., D.B.), Public Health England, London; Aerogen, Galway, Ireland (J.B.F.); and Sainte-Foy-lès-Lyon, France (M.G.).

BACKGROUND:

Aerosolized vaccine can be used as a needle-free method of immunization against measles, a disease that remains a major cause of illness and death. Data on the immunogenicity of aerosolized vaccine against measles in children are inconsistent.

METHODS:

We conducted an open-label noninferiority trial involving children 9.0 to 11.9 months of age in India who were eligible to receive a first dose of measles vaccine. Children were randomly assigned to receive a single dose of vaccine by means of either aerosol inhalation or a subcutaneous injection. The primary end points were seropositivity for antibodies against measles and adverse events 91 days after vaccination. The noninferiority margin was 5 percentage points.

RESULTS:

A total of 1001 children were assigned to receive aerosolized vaccine, and 1003 children were assigned to receive subcutaneous vaccine; 1956 of all the children (97.6%) were followed to day 91, but outcome data were missing for 331 children because of thawed specimens. In the per-protocol population, data on 1560 of 2004 children (77.8%) could be evaluated. At day 91, a

total of 662 of 775 children (85.4%; 95% confidence interval [CI], 82.5 to 88.0) in the aerosol group, as compared with 743 of 785 children (94.6%; 95% CI, 92.7 to 96.1) in the subcutaneous group, were seropositive, a difference of -9.2 percentage points (95% CI, -12.2 to -6.3). Findings were similar in the full-analysis set (673 of 788 children in the aerosol group [85.4%] and 754 of 796 children in the subcutaneous group [94.7%] were seropositive at day 91, a difference of -9.3 percentage points [95% CI, -12.3 to -6.4]) and after multiple imputation of missing results. No serious adverse events were attributable to measles vaccination. Adverse-event profiles were similar in the two groups.

CONCLUSIONS:

Aerosolized vaccine against measles was immunogenic, but, at the prespecified margin, the aerosolized vaccine was inferior to the subcutaneous vaccine with respect to the rate of seropositivity. (Funded by the Bill and Melinda Gates Foundation; Measles Aerosol Vaccine Project Clinical Trials Registry-India number, CTRI/2009/091/000673.).

Meningococcal vaccine

Vaccine. 2014 Jul 16;32(33):4220-7. doi: 10.1016/j.vaccine.2014.04.052. Epub 2014 May 23.

The impact of pre-existing antibody on subsequent immune responses to meningococcal A-containing vaccines.

Idoko OT[1], Okolo SN[2], Plikaytis B[3], Akinsola A[4], Viviani S[5], Borrow R[6], Carlone G[3], Findlow H[6], Elie C[3], Kulkarni PS[7], Preziosi MP[8], Ota M[9], Kampmann B[10].

Medical Research Council Unit, The Gambia. ; Jos University Teaching Hospital, P.M.B. 2084, Jos, Nigeria.; Centers for Disease Control and Prevention, Atlanta, USA.; Medical Research Council Unit, , The Gambia.; Meningitis Vaccine Project (MVP), PATH Europe, France.; Vaccine Evaluation Unit, Public Health England, Manchester Royal Infirmary, Manchester, UK.; Serum Institute of India Ltd., 212/2, Hadapsar, Pune, India.; MVP, World Health Organization, Geneva, Switzerland.; Medical Research Council Unit, The Gambia; WHO regional Office for Africa, Brazzaville, Congo.; Medical Research Council Unit The Gambia; Academic Department of Paediatrics, Imperial College London, London W2 1NY, UK.

Abstract

Major epidemics of serogroup A meningococcal meningitis continue to affect the African meningitis belt. The development of an affordable conjugate vaccine against the disease became a priority for World Health Organization (WHO) in the late 1990s. Licensing of meningococcal vaccines has been based on serological correlates of protection alone, but such correlates might differ in different geographical regions. If high pre-vaccination antibody concentrations/titers impacts on the response to vaccination and possibly vaccine efficacy, is not clearly understood. We set out to define the pre-vaccination Meningococcal group A (Men A) antibody concentrations/titers in The Gambia and study their impact on the immunogenicity of Men A containing vaccines. Data from subjects originally enrolled in studies to test the safety and immunogenicity of the MenA vaccine recently developed for Africa meningococcal A polysaccharide conjugated to tetanus toxoid, MenAfriVac(®) (PsA-TT) were analyzed. Participants had been randomized to receive either the study vaccine PsA-TT or the reference quadrivalent plain polysaccharide vaccine containing meningococcal groups A, C, W, and Y, Mencevax(®) ACWY, GlaxoSmithKline (PsACWY) in a 2:1 ratio. Venous blood samples were collected before and 28 days after vaccination. Antibodies were assayed by enzyme-linked

immunosorbent assay (ELISA) for geometric mean concentrations and serum bactericidal antibody (SBA) for functional antibody. The inter age group differences were compared using ANOVA and the pre and post-vaccination differences by t test. Over 80% of the ≥19 year olds had pre-vaccination antibody concentrations above putatively protective concentrations as compared to only 10% of 1-2 year olds. Ninety-five percent of those who received the study vaccine had ≥4-fold antibody responses if they had low pre-vaccination concentrations compared to 76% of those with high pre-vaccination concentrations. All subjects with low pre-vaccination titers attained ≥4-fold responses as compared to 76% with high titers where study vaccine was received. Our data confirm the presence of high pre-vaccination Men A antibody concentrations/titers within the African meningitis belt, with significantly higher concentrations in older individuals. Although all participants had significant increase in antibody levels following vaccination, the four-fold or greater response in antibody titers were significantly higher in individuals with lower pre-existing antibody titers, especially after receiving PsA-TT. This finding may have some implications for vaccination strategies adopted in the future.

Pneumococcal vaccine

Lancet Infect Dis. 2015 Apr;15(4):405-14. doi: 10.1016/S1473-3099(15)70007-1. Epub 2015 Feb 18.

Comparison of two-dose priming plus 9-month booster with a standard three-dose priming schedule for a ten-valent pneumococcal conjugate vaccine in Nepalese infants: a randomised, controlled, open-label, non-inferiority trial.

Hamaluba M[1], Kandasamy R[2], Upreti SR[3], Subedi GR[4], Shrestha S[5], Bhattarai S[5], Gurung M[5], Pradhan R[5], Voysey M[6], Gurung S[7], Pradhan S[5], Thapa AK[5], Maharjan R[5], Kiran U[5], Kerridge SA[1], Hinds J[8], van der Klis F[9], Snape MD[1], Murdoch DR[10], Kelly S[1], Kelly DF[1], Adhikari N[5], Thorson S[5], Pollard AJ[1].

Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford, UK.; Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford, UK. ; Child Health Division, Department of Health Services, Ministry of Health, Kathmandu, Nepal.; National Immunization Program, Department of Health Services, Ministry of Health, Kathmandu, Nepal.; Paediatric Research Unit, Patan Academy of Health Sciences, Kathmandu, Nepal.; Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.; Programme for Immunization Preventable Diseases, World Health Organization, Kathmandu, Nepal.; Division of Clinical Sciences, St George's, University of London, London, UK.National Institute for Public Health and the Environment, Bilthoven, Utrecht, The Netherlands.; Department of Pathology, University of Otago, Christchurch, New Zealand.

BACKGROUND:

Use of pneumococcal conjugate vaccines (PCVs) in resource-poor countries has focused on early infant immunisation with little emphasis on protection in late infancy and beyond. Boosting of the immune response later in infancy might provide improved persistence of immunogenicity into early childhood, however data are scarce. The aim of this study was to investigate if a two-dose prime with booster at age 9 months compared with a three-dose prime-

only PCV schedule provided non-inferior immunogenicity in early infancy and superior persistence of antibody responses in early childhood.

METHODS:

We did an open-label, randomised, parallel group, controlled trial in healthy infants aged 40-60 days from Kathmandu, Nepal. Participants were randomly allocated (4:4:5 ratio) to receive PCV10 in addition to routine immunisations either as a two-dose prime and boost (2+1), three-dose prime (3+0), or two doses after completion of the initial study phase (0+2). We used a computer generated randomisation list with randomly varying block sizes. We followed up participants at age 2-4 years together with a group of unvaccinated controls. Sera were analysed for opsonophagocytic activity, protein D, and PCV10 serotype-specific IgG. Laboratory staff was masked to intervention group assignment. The primary outcome measure was to determine the proportion of participants in the 2+1 group at age 10 months with specific IgG for serotypes 1, 5, and 14 of at least 0·2 μg/mL in the per-protocol population. The secondary outcomes were non-inferiority (within 10% levels) at age 18 weeks for the proportion of participants in the 2+1 group compared with the 3+0 group with serotypes 1, 5, and 14 specific IgG of at least 0·2 μg/mL; the proportion of participants with PCV10 serotype-specific IgG of at least 0·2 μg/mL and opsonophagocytic activity reciprocal titre of at least 8 at ages 18 weeks and 10 months; and nasopharyngeal pneumococcal serotype-specific carriage rates at age 9 months in each study group. In the follow-up study, the primary outcome measure was the proportion of participants with IgG of at least 0·2 μg/mL for PCV10 serotypes at age 2-4 years in children previously immunised with a 3+0 schedule compared with a 2+1 schedule. The trial is registered with Current Controlled Trials, registration number ISRCTN56766232.

FINDINGS:

Between May 10, 2010, and Jan 7, 2011, 390 children were randomly assigned to each group: 119 to the 2+1 group, 120 to the 3+0 group, and 151 to the 0+2 group. At age 10 months, the proportions of 2+1 participants with IgG of at least 0·2 μg/mL were 99·0% (95% CI 94·2-100·0) for serotype 1, 100% (96·2-100·0) for serotype 5, and 97·9% (92·5-99·7) for serotype 14. At age 18 weeks, non-inferiority (within 10% levels) of the 2+1 group was shown compared with the 3+0 group, and there was no difference between the 2+1 and 3+0 groups for the proportion with IgG of at least 0·2 μg/mL for any of the PCV10 serotypes. At age 10 months, proportions with IgG of at least 0·2 μg/mL for serotypes 1, 5, 6B, and 23F, were higher in the 2+1 group than in the 3+0 group. At age 18 weeks, there were no differences in opsonophagocytic activity between the 2+1 and 3+0 groups for reciprocal titres of at least 8, but at age 10 months, proportions with an opsonophagocytic reciprocal titre of at least 8 for serotypes 1, 4, 5, 6B, 18C, 19F and 23F were higher in the 2+1 group than in the 3+0 group. At age 2-4 years, there were higher proportions in the 2+1 group versus the 3+0 group with IgG of at least 0·2 μg/mL for serotypes 1, 5, 6B, and 18C.

INTERPRETATION:

Use of a 2+1 PCV schedule with booster at age 9 months in a resource-poor setting improved antibody persistence through early childhood without compromising antibody responses in early infancy. This schedule is now recommended by WHO for progressive introduction across Nepal, with PCV10 introduction having commenced on Jan 18, 2015. Concurrent pre-implementation and post-implementation surveillance is being done by a GAVI Alliance funded study.

http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(15)70007-1.pdf

BMC Infect Dis. 2014 Oct 2;14:530. doi: 10.1186/1471-2334-14-530.

A randomised trial to evaluate the immunogenicity, reactogenicity, and safety of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) co-administered with routine childhood vaccines in Singapore and Malaysia.

Lim FS[1], Koh MT, Tan KK, Chan PC, Chong CY, Shung Yehudi YW, Teoh YL, Shafi F, Hezareh M, Swinnen K, Borys D.

National Healthcare Group Polyclinics, Singapore

BACKGROUND:

The immunogenicity, reactogenicity, and safety of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) co-administered with routine childhood vaccines were evaluated among infants from Singapore and Malaysia, where PHiD-CV has been licensed.

METHODS:

In the primary vaccination phase, 298 infants from Singapore and 168 infants from Malaysia were randomised to receive the Phase III Clinical (Clin) or the Commercial (Com) lot of PHiD-CV at 2, 3, and 5 months of age. In the booster vaccination phase, 238 toddlers from Singapore received one dose of the PHiD-CV Commercial lot at 18-21 months of age. Immune responses to pneumococcal polysaccharides were measured using 22F-inhibition enzyme-linked immunosorbent assay (ELISA) and functional opsonophagocytic activity (OPA) assay and to protein D, using ELISA.

RESULTS:

Immune responses induced by primary vaccination with the PHiD-CV Commercial lot were non-inferior to the Phase III Clinical lot in terms of adjusted antibody geometric mean concentration (GMC) ratios for each vaccine pneumococcal serotype and protein D. For each vaccine pneumococcal serotype, ≥93.6% and ≥88.5% of infants from Malaysia and Singapore had post-primary vaccination antibody concentrations ≥0.2 μg/mL and OPA titres ≥8, in the Clin and Com groups, respectively. For each vaccine pneumococcal serotype, ≥60.8% and ≥98.2% of toddlers from Singapore had pre- and post-booster antibody concentrations ≥0.2 μg/mL, in the Clin and Com groups, respectively. All children, except one, had measurable anti-protein D antibodies and the primary and booster doses of the co-administered vaccines were immunogenic. The incidence of each grade 3 solicited symptom was ≤11.1% in both study phases. No serious adverse events considered causally related to vaccination were reported throughout the study.

CONCLUSIONS:

PHiD-CV given as three-dose primary vaccination to infants in Singapore and Malaysia and booster vaccination to toddlers in Singapore was shown to be immunogenic with a clinically acceptable-safety profile.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4286912/pdf/12879_2014_Article_3854.pdf

Polio vaccine

Lancet. 2014 Oct 25;384(9953):1505-12. doi: 10.1016/S0140-6736(14)60934-X. Epub 2014 Jul 10.

Effect of a single inactivated poliovirus vaccine dose on intestinal immunity against poliovirus in children previously given oral vaccine: an open-label, randomised controlled trial.

John J[1], Giri S[1], Karthikeyan AS[1], Iturriza-Gomara M[2], Muliyil J[1], Abraham A[1], Grassly NC[3], Kang G[1].

Christian Medical College, Vellore, Tamil Nadu, India.; Christian Medical College, Vellore, Tamil Nadu, India; Institute of Infection and Global Health, University of Liverpool, Liverpool, UK.; Christian Medical College, Vellore, Tamil Nadu, India; Department of Infectious Disease Epidemiology, Imperial College London, London, UK.

BACKGROUND:

Intestinal immunity induced by oral poliovirus vaccine (OPV) is imperfect and wanes with time, permitting transmission of infection by immunised children. Inactivated poliovirus vaccine (IPV) does not induce an intestinal mucosal immune response, but could boost protection in children who are mucosally primed through previous exposure to OPV. We aimed to assess the effect of IPV on intestinal immunity in children previously vaccinated with OPV.

METHODS:

We did an open-label, randomised controlled trial in children aged 1-4 years from Chinnallapuram, Vellore, India, who were healthy, had not received IPV before, and had had their last dose of OPV at least 6 months before enrolment. Children were randomly assigned (1:1) to receive 0·5 mL IPV intramuscularly (containing 40, 8, and 32 D antigen units for serotypes 1, 2, and 3) or no vaccine. The randomisation sequence was computer generated with a blocked randomisation procedure with block sizes of ten by an independent statistician. The laboratory staff did blinded assessments. The primary outcome was the proportion of children shedding poliovirus 7 days after a challenge dose of serotype 1 and 3 bivalent OPV (bOPV). A second dose of bOPV was given to children in the no vaccine group to assess intestinal immunity resulting from the first dose. A per-protocol analysis was planned for all children who provided a stool sample at 7 days after bOPV challenge. This trial is registered with Clinical Trials Registry of India, number CTRI/2012/09/003005.

FINDINGS:

Between Aug 19, 2013, and Sept 13, 2013, 450 children were enrolled and randomly assigned into study groups. 225 children received IPV and 225 no vaccine. 222 children in the no vaccine group and 224 children in the IPV group had stool samples available for primary analysis 7 days after bOPV challenge. In the IPV group, 27 (12%) children shed serotype 1 poliovirus and 17 (8%) shed serotype 3 poliovirus compared with 43 (19%) and 57 (26%) in the no vaccine group (risk ratio 0·62, 95% CI 0·40-0·97, p=0·0375; 0·30, 0·18-0·49, p<0·0001). No adverse events were related to the study interventions.

INTERPRETATION:

The substantial boost in intestinal immunity conferred by a supplementary dose of IPV given to children younger than 5 years who had previously received OPV shows a potential role for this

vaccine in immunisation activities to accelerate eradication and prevent outbreaks of poliomyelitis.

Science. 2014 Aug 22;345(6199):922-5. doi: 10.1126/science.1255006.

Polio eradication. Efficacy of inactivated poliovirus vaccine in India.

Jafari H[1], Deshpande JM[2], Sutter RW[3], Bahl S[1], Verma H[4], Ahmad M[1], Kunwar A[1], Vishwakarma R[1], Agarwal A[1], Jain S[5], Estivariz C[6], Sethi R[1], Molodecky NA[4], Grassly NC[7], Pallansch MA[6], Chatterjee A[5], Aylward RB[4].

World Health Organization, India-National Polio Surveillance Project, R. K. New Delhi India.; Enterovirus Research Center, Haffkine Institute Compound, Parel, Mumbai, India.; World Health Organization, Ave Appia, Geneva, Switzerland..; Panacea Biotec Ltd., New Delhi, India.; Centers for Disease Control and Prevention, Atlanta, GA, USA.; Department of Infectious Disease Epidemiology, Imperial College London, London, UK.

Abstract

Inactivated poliovirus vaccine (IPV) is efficacious against paralytic disease, but its effect on mucosal immunity is debated. We assessed the efficacy of IPV in boosting mucosal immunity. Participants received IPV, bivalent 1 and 3 oral poliovirus vaccine (bOPV), or no vaccine. A bOPV challenge was administered 4 weeks later, and excretion was assessed 3, 7, and 14 days later. Nine hundred and fifty-four participants completed the study. Any fecal shedding of poliovirus type 1 was 8.8, 9.1, and 13.5% in the IPV group and 14.4, 24.1, and 52.4% in the control group by 6- to 11-month, 5-year, and 10-year groups, respectively (IPV versus control: Fisher's exact test $P < 0.001$). IPV reduced excretion for poliovirus types 1 and 3 between 38.9 and 74.2% and 52.8 and 75.7%, respectively. Thus, IPV in OPV-vaccinated individuals boosts intestinal mucosal immunity.

http://www.sciencemag.org/content/345/6199/922.full.pdf

Rotavirus vaccine

Vaccine. 2014 Aug 11;32 Suppl 1:A134-9. doi: 10.1016/j.vaccine.2014.04.078.

Effect of withholding breastfeeding on the immune response to a live oral rotavirus vaccine in North Indian infants.

Rongsen-Chandola T[1], Strand TA[2], Goyal N[1], Flem E[3], Rathore SS[1], Arya A[1], Winje BA[4], Lazarus R[5], Shanmugasundaram E[5], Babji S[5], Sommerfelt H[6], Vainio K[7], Kang G[5], Bhandari N[1].

Centre for Health Research and Development, Society for Applied Studies India.; Innlandet Hospital Trust, Lillehammer, Norway; Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway. ; Department of Vaccines, Division of Infectious Disease Control, Norwegian Institute of Public Health Oslo, Norway.; Department of Infectious Diseases Epidemiology, Division of Infectious Disease Control, Norwegian Institute of Public Health Oslo, Norway.; The Wellcome Trust Research Laboratory, Christian Medical College, Tamil Nadu, India.; Department of Vaccines, Division of Infectious Disease Control, Norwegian Institute of Public Health Oslo, Norway; Department of International Public Health, Norwegian Institute of Public Health, Oslo, Norway.;

Department of Virology, Division of Infectious Disease Control, Norwegian Institute of Public Health Oslo, Norway.

Abstract

Interference from transplacental and breast milk antibodies may impede the performance of oral live vaccines. The effect of breastfeeding on the immunogenicity of Rotarix, a two-dose oral monovalent rotavirus vaccine, was examined in a community-based trial in New Delhi, India. Four hundred mother-infant pairs were randomized into two equal groups. Infants were aged 6-7 weeks at enrollment. Mothers were encouraged to either breastfeed or to withhold breastfeeding during the 30 min prior to and after each vaccine dose was administered. We collected blood specimens from infants at enrollment and 4 weeks after the second vaccine dose. Blood and breast milk specimens were obtained from mothers at baseline and breast milk specimens were collected at the time of the second vaccine dose. Seroconversion was defined as infant serum anti-VP6 IgA antibody level of ≥20 IU/mL 4 weeks after the second vaccine dose and a ≥4-fold rise from baseline. There was no difference in the proportion who seroconverted between the two groups (26% vs 27%; p=0.92). The levels of infant serum IgA, maternal serum and breast milk IgA and IgG anti-rotavirus antibodies predicted the anti-rotavirus IgA level in infants at end-study and explained approximately 10% of the variability of the immune response (r(2)=0.10, p<0.001). In this population, the immune response to Rotarix was not enhanced by withholding breastfeeding around the time of vaccination. Maternal anti-rotavirus antibodies explained little of the variability in the immune response to the vaccine. Factors other than maternal anti-rotavirus antibodies probably explain why infants in low-and middle-income settings respond poorly to live oral rotavirus vaccines.

Vaccine. 2014 Aug 11;32 Suppl 1:A129-33. doi: 10.1016/j.vaccine.2014.03.002.

Immunogenicity of a three dose and five dose oral human rotavirus vaccine (RIX4414) schedule in south Indian infants.

Kompithra RZ[1], Paul A[2], Manoharan D[2], Babji S[2], Sarkar R[2], Mathew LG[1], Kang G[3].

Department of Paediatrics, Christian Medical College, Vellore, India.; Department of Gastrointestinal Sciences, Christian Medical College, Vellore, India.

AIM:

This study was undertaken to compare the immunogenicity of a three dose and five dose schedule of an oral live-attenuated human rotavirus vaccine, Rotarix in south Indian infants.

METHOD:

Healthy infants (N=90), six to seven weeks of age were enrolled to receive three doses (n=45) or five doses of Rotarix vaccine (n=45) along with other scheduled vaccines, each dose separated by a four week interval. Blood samples were taken before vaccination and one month post-dose three in the Rotarix three dose group and one month post-dose five in the Rotarix five dose group; all were tested for anti-rotavirus IgA by an antibody sandwich enzyme immunoassay.

RESULTS:

At baseline, >50% of infants had >20 units of anti-rotavirus IgA. The seroconversion rates after three and five doses were low and not significantly different in the two groups. However, among vaccine responders, children seropositive at baseline showed a much greater absolute increase in IgA antibody levels than children seronegative at baseline.

CONCLUSIONS:

Rotarix vaccine showed low immunogenicity in south Indian children and increasing the number of doses did not increase the proportion of infants seroconverting after vaccination.

Vaccine. 2014 Aug 11;32 Suppl 1:A117-23. doi: 10.1016/j.vaccine.2014.03.069.

Evaluation of safety and immunogenicity of a live attenuated tetravalent (G1-G4) Bovine-Human Reassortant Rotavirus vaccine (BRV-TV) in healthy Indian adults and infants.

Dhingra MS[1], Kundu R[2], Gupta M[3], Kanungo S[4], Ganguly N[2], Singh MP[3], Bhattacharya MK[4], Ghosh R[2], Kumar R[3], Sur D[4], Chadha SM[5], Saluja T[5].

Shantha Biotechnics Ltd., Hyderabad, India.; Institute of Child Health, Kolkata, India.; Postgraduate Institute of Medical Education and Research, Chandigarh, India.; National Institute of Cholera and Enteric Diseases, Kolkata, India.; Shantha Biotechnics Ltd., Hyderabad, India.

BACKGROUND:

Rotavirus infections, prevalent in human populations worldwide are mostly caused by Group A viruses. Live attenuated rotavirus vaccines are highly effective in preventing severe rotavirus gastroenteritis. However, the cost of these vaccines and local availability can be a barrier for widespread adoption in public health programs in developing countries where infants suffer a heavy burden of rotavirus related morbidity and mortality. A phase I/II study was carried out with the long term aim to produce a locally licensed vaccine which is equally safe and immunogenic as compared to available licensed vaccines.

METHODS:

This study was conducted in two cohorts. In the first cohort, 20 healthy adults were administered a single dose of the rotavirus vaccine (highest antigen concentration planned for infants) or placebo and were followed up for 10 days for safety. Following demonstration of safety in adult volunteers, 100 healthy infants were recruited (cohort 2) and randomly divided into five equal study groups. They were administered three doses of either the investigational rotavirus vaccine (BRV-TV) at one of the three antigen concentrations or Rotateq or Placebo at 6-8, 10-12 and 14-16 weeks of age. All infants were followed up for safety till 28 days after the third dose. Immune response to the vaccine, in terms of seroresponse and geometric mean concentrations, was compared across the five study groups.

RESULTS:

Increase in anti-rotavirus serum IgA antibodies from baseline, demonstrated higher immune response for all the three antigen concentrations of BRV-TV vaccine and RotaTeq in comparison with the placebo. Sero-response rates for placebo, BRV-TV dose-levels 10(5.0) FFU, 10(5.8) FFU, 10(6.4) FFU, and Rotateq at 28 days post third dose were 11.1%, 27.8%, 41.2%, 83.3%, and 63.2% respectively using the four-fold or more criteria. The BRV-TV vaccine arm corresponding to the highest antigen concentration of 10(6.4) FFU had a higher sero-response rate compared to the active comparator arm (RotaTeq), 28 days post each vaccine dose. The safety profile was comparable across the treatment groups.

CONCLUSIONS:

Overall, the results showed that all three doses of BRV-TV vaccine were safe, well tolerated and displayed good immunogenicity (dose-response) in healthy Indian infants.

Vaccine. 2014 Aug 11;32 Suppl 1:A110-6. doi: 10.1016/j.vaccine.2014.04.079.

Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life.

Bhandari N[1], Rongsen-Chandola T[1], Bavdekar A[2], John J[3], Antony K[4], Taneja S[1], Goyal N[1], Kawade A[2], Kang G[3], Rathore SS[1], Juvekar S[2], Muliyil J[3], Arya A[1], Shaikh H[2], Abraham V[3], Vrati S[5], Proschan M[6], Kohberger R[7], Thiry G[8], Glass R[6], Greenberg HB[9], Curlin G[6], Mohan K[10], Harshavardhan GV[10], Prasad S[10], Rao TS[11], Boslego J[12], Bhan MK[13]; India Rotavirus Vaccine Group.

Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.;KEM Hospital Research Centre, Pune, Maharashtra, India; Christian Medical College, Vellore, Tamil Nadu, India.; PATH-India, India; Translational Health Science and Technology Institute, Gurgaon, Haryana, India; National Institute of Immunology, New Delhi, India.; National Institutes of Health, Bethesda, MD, USA.; Blair & Co, Greenwich, CT, USA.; Advancing Rotavirus Vaccines Development Project, PATH, France.; Stanford University School of Medicine, USA.; Bharat Biotech International Limited, Genome Valley, Andhra Pradesh, India.; Department of Biotechnology, Ministry of Science and Technology, Government of India, India.; Vaccine Development Global Program, PATH, USA.; Ministry of Science and Technology, Government of India, India.

Abstract

Rotavirus gastroenteritis is one of the leading causes of diarrhea in Indian children less than 2 years of age. The 116E rotavirus strain was developed as part of the Indo-US Vaccine Action Program and has undergone efficacy trials. This paper reports the efficacy and additional safety data in children up to 2 years of age. In a double-blind placebo controlled multicenter trial, 6799 infants aged 6-7 weeks were randomized to receive three doses of an oral human-bovine natural reassortant vaccine (116E) or placebo at ages 6, 10, and 14 weeks. The primary outcome was severe (≥11 on the Vesikari scale) rotavirus gastroenteritis. Efficacy outcomes and adverse events were ascertained through active surveillance. We randomly assigned 4532 and 2267 subjects to receive vaccine and placebo, respectively, with over 96% subjects receiving all three doses of the vaccine or placebo. The per protocol analyses included 4354 subjects in the vaccine and 2187 subjects in the placebo group. The overall incidence of severe RVGE per 100 person years was 1.3 in the vaccine group and 2.9 in the placebo recipients. Vaccine efficacy against severe rotavirus gastroenteritis in children up to 2 years of age was 55.1% (95% CI 39.9 to 66.4; p<0.0001); vaccine efficacy in the second year of life of 48.9% (95% CI 17.4 to 68.4; p=0.0056) was only marginally less than in the first year of life [56.3% (95% CI 36.7 to 69.9; p<0.0001)]. The number of infants needed to be immunized to prevent one episode of severe RVGE in the first 2 years of life was 40 (95% CI 28.0 to 63.0) and for RVGE of any severity, it was 21 (95% CI 16.0 to 32.0). Serious adverse events were observed at the same rates in the two groups. None of the eight intussusception events occurred within 30 days of a vaccine dose and all were reported only after the third dose. The sustained efficacy of the 116E in the second year of life is reassuring.

Vaccine. 2014 Aug 11;32 Suppl 1:A104-9. doi: 10.1016/j.vaccine.2014.03.036.

Active surveillance for intussusception in a phase III efficacy trial of an oral monovalent rotavirus vaccine in India.

John J[1], Kawade A[2], Rongsen-Chandola T[3], Bavdekar A[2], Bhandari N[3], Taneja S[3], Antony K[4], Bhatnagar V[5], Gupta A[5], Kabra M[5], Kang G[6].

Christian Medical College, Vellore, India.; KEM Hospital Research Centre, Pune, India.; Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.; PATH, India.; All India Institute of Medical Sciences, New Delhi, India.; Christian Medical College, Vellore, India.

BACKGROUND:

Post licensure studies have identified an increased risk of intussusception following vaccination with currently licensed rotavirus vaccines, raising safety concerns generic to all rotavirus vaccines. We describe the surveillance for intussusception in a phase III clinical trial with an oral monovalent rotavirus vaccine developed from the neonatal 116E strain.

METHODS:

Using broad screening criteria and active surveillance, the incidence of intussusception between 6 weeks and 2 years of age was measured in 4532 children who received three doses of vaccine and 2267 children who received a placebo in the clinical trial. Possible intussusceptions were evaluated with a screening ultrasonogram. An independent intussusception case adjudication committee reviewed all intussusceptions and graded them on Brighton Collaboration criteria for diagnostic certainty.

RESULTS:

We identified twenty-three intussusceptions on ultrasound from 1361 evaluated sentinel events. Eleven were of level 1 diagnostic certainty as determined by the independent intussusception case adjudication committee. None required surgical intervention, and the earliest identified intussusception was at 36 days following the third dose in a placebo recipient. Among vaccine recipients the first event of intussusception occurred 112 days after the third dose. The incidence of ultrasound-diagnosed intussusception was 200/100,000 child-years (95% CI, 120, 320) among those receiving the vaccine and 141/100,000 child-years (95% CI, 50, 310) among those receiving the placebo. The incidence rate of confirmed intussusception among vaccine recipients was 94/100,000 child-years (95% CI, 41, 185) and 71/100,000 child-years (95% CI, 15, 206) among those receiving the placebo.

CONCLUSION:

In this licensure study, 23 cases of intussusception were identified through an active surveillance system, but there was no temporal association with rotavirus vaccination. The use of active surveillance with broad criteria intended for ensuring safety of children participating in a trial, identified several transient intussusceptions that were of doubtful clinical significance.

J Infect Dis. 2014 Dec 1;210(11):1772-9. doi: 10.1093/infdis/jiu335. Epub 2014 Jun 16.

Impact of different dosing schedules on the immunogenicity of the human rotavirus vaccine in infants in Pakistan: a randomized trial.

Randomised trials in child health in developing countries 2014-15

Ali SA[1], Kazi AM[1], Cortese MM[2], Fleming JA[3], Parashar UD[2], Jiang B[2], McNeal MM[4], Steele D[5], Bhutta Z[1], Zaidi A[1].

Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan.; Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.; Vaccine Access and Delivery, Program for Appropriate Technology in Health (PATH), Seattle, Washington.; Department of Pediatrics, Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Ohio.; Vaccine Access and Delivery, Program for Appropriate Technology in Health (PATH), Seattle, Washington Now With The Bill & Melinda Gates Foundation, Seattle, Washington.

BACKGROUND:

Current oral rotavirus vaccines perform suboptimally in resource-poor settings. We investigated the effect of an additional dose and later schedule on the immunogenicity of monovalent rotavirus vaccine (RV1) in a developing country.

METHODS:

Infants received RV1 at 6 and 10, 10 and 14, or 6, 10, and 14 weeks of age. The primary objective was to compare antirotavirus immunoglobulin A (IgA) seroconversion at 18 weeks in the 6/10/14 arm to the cumulative seroconversion (highest result at 14 or 18 weeks) in the 6/10 arm.

RESULTS:

Overall, 480 (76.2%) of 630 randomized infants completed the trial per protocol. Seroconversion in the 6/10/14 arm was 36.7% (95% CI, 29.8, 44.2) compared to 36.1% (CI, 29.0, 43.9) in the 6/10 arm, (P=1.0); the result from the 10/14 arm was 38.5% (CI, 31.2, 46.3). Seroconversion in the 6/10 arm at 14 weeks (post hoc) was lower at 29.7% (CI, 23.1, 37.3).

CONCLUSIONS:

In Pakistani infants, the immunogenicity of RV1 did not increase significantly with 3 doses at 6, 10, and 14 weeks compared to 2 doses at 6 and 10 weeks. Additional strategies should be evaluated for improving rotavirus vaccine immunogenicity in high burden countries.

Tuberculosis vaccine

Vaccine. 2014 Oct 14;32(45):5908-17. doi: 10.1016/j.vaccine.2014.09.001. Epub 2014 Sep 10.

The novel tuberculosis vaccine, AERAS-402, is safe in healthy infants previously vaccinated with BCG, and induces dose-dependent CD4 and CD8T cell responses.

Kagina BM[1], Tameris MD[2], Geldenhuys H[2], Hatherill M[2], Abel B[3], Hussey GD[1], Scriba TJ[2], Mahomed H[4], Sadoff JC[5], Hanekom WA[6]; 018-402 Clinical Lab study team, Mansoor N, Hughes J, de Kock M, Whatney W, Africa H, Krohn C, Veldsman A, Kany AL, Douoguih M, Pau MG, Hendriks J, McClainc B, Benko J, Snowden MA, Hokey DA.

South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; Vaccines for Africa Initiative, Division of Medical Microbiology &

Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa.; South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa.; South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore.; South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; Western Cape Government and Stellenbosch University, Cape Town, South Africa.; Crucell Holland BV, , The Netherlands; South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; Bill and Melinda Gates Foundation, Seattle, WA, USA.

BACKGROUND:

Efforts to reduce risk of tuberculosis disease in children include development of effective vaccines. Our aim was to test safety and immunogenicity of the new adenovirus 35-vectored tuberculosis vaccine candidate AERAS-402 in infants, administered as a boost following a prime with the Bacille Calmette-Guerin vaccine.

METHODS:

In a phase 1 randomised, double-blind, placebo-controlled, dose-escalation trial, BCG-vaccinated infants aged 6-9 months were sequentially assigned to four study groups, then randomized to receive an increasing dose-strength of AERAS-402, or placebo. The highest dose group received a second dose of vaccine or placebo 56 days after the first. The primary study outcome was safety. Whole blood intracellular cytokine staining assessed immunogenicity.

RESULTS:

Forty-two infants received AERAS-402 and 15 infants received placebo. During follow-up of 182 days, an acceptable safety profile was shown with no serious adverse events or discontinuations related to the vaccine. AERAS-402 induced a specific T cell response. A single dose of AERAS-402 induced CD4T cells predominantly expressing single IFN-γ whereas two doses induced CD4T cells predominantly expressing IFN-γ, TNF-α and IL-2 together. CD8T cells were induced and were more likely to be present after 2 doses of AERAS-402.

CONCLUSIONS:

AERAS-402 was safe and immunogenic in healthy infants previously vaccinated with BCG at birth. Administration of the highest dose twice may be the most optimal vaccination strategy, based on the induced immunity. Multiple differences in T cell responses when infants are compared with adults vaccinated with AERAS-402, in the same setting and using the same whole blood intracellular cytokine assay, suggest specific strategies may be important for vaccination for each population.

Clin Vaccine Immunol. 2014 Jul;21(7):1005-11. doi: 10.1128/CVI.00128-14. Epub 2014 May 14.

Process of assay selection and optimization for the study of case and control samples from a phase IIb efficacy trial of a candidate tuberculosis vaccine, MVA85A.

Harris SA[1], Satti I[2], Matsumiya M[2], Stockdale L[2], Chomka A[2], Tanner R[2], O'Shea MK[2], Manjaly Thomas ZR[2], Tameris M[3], Mahomed H[4], Scriba TJ[3], Hanekom WA[3], Fletcher HA[2], McShane H[1].

Jenner Institute, University of Oxford, Oxford, United Kingdom ; South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine and School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.; Division of Community Health, Stellenbosch University, Cape Town, South Africa Metropolitan District Health Services, Western Cape Government, Cape Town, South Africa.

Abstract

The first phase IIb safety and efficacy trial of a new tuberculosis vaccine since that for BCG was completed in October 2012. BCG-vaccinated South African infants were randomized to receive modified vaccinia virus Ankara, expressing the Mycobacterium tuberculosis antigen 85A (MVA85A), or placebo. MVA85A did not significantly boost the protective effect of BCG. Cryopreserved samples provide a unique opportunity for investigating the correlates of the risk of tuberculosis disease in this population. Due to the limited amount of sample available from each infant, preliminary work was necessary to determine which assays and conditions give the most useful information. Peripheral blood mononuclear cells (PBMC) were stimulated with antigen 85A (Ag85A) and purified protein derivative from M. tuberculosis in an ex vivo gamma interferon (IFN-γ) enzyme-linked immunosorbent spot assay (ELISpot) and a Ki67 proliferation assay. The effects of a 2-h or overnight rest of thawed PBMC on ELISpot responses and cell populations were determined. Both the ELISpot and Ki67 assays detected differences between the MVA85A and placebo groups, and the results correlated well. The cell numbers and ELISpot responses decreased significantly after an overnight rest, and surface flow cytometry showed a significant loss of CD4(+) and CD8(+) T cells. Of the infants tested, 50% had a positive ELISpot response to a single pool of flu, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) (FEC) peptides. This pilot work has been essential in determining the assays and conditions to be used in the correlate study. Moving forward, PBMC will be rested for 2 h before assay setup. The ELISpot assay, performed in duplicate, will be selected over the Ki67 assay, and further work is needed to evaluate the effect of high FEC responses on vaccine-induced immunity and susceptibility to tuberculosis disease.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097435/pdf/zcd1005.pdf

J Infect Dis. 2015 Feb 1;211(3):338-46. doi: 10.1093/infdis/jiu434. Epub 2014 Aug 8.

Delaying BCG vaccination until 8 weeks of age results in robust BCG-specific T-cell responses in HIV-exposed infants.

Tchakoute CT[1], Hesseling AC[2], Kidzeru EB[1], Gamieldien H[3], Passmore JA[4], Jones CE[5], Gray CM[6], Sodora DL[7], Jaspan HB[8].

Division of Immunology.; Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town.; Division of Immunology Division of Medical Virology.; Division of Medical Virology National Health Laboratory Services, South Africa.; Institute of Infectious Disease and Molecular Medicine, Department of Clinical Laboratory Sciences, University of Cape Town Paediatric

Infectious Diseases Research Group, St George's, University of London, United Kingdom.; Division of Immunology National Health Laboratory Services, South Africa.; Seattle Biomedical Research Institute, Washington.; Division of Immunology Seattle Biomedical Research Institute, Washington.

BACKGROUND:

BCG vaccination prevents disseminated tuberculosis in children, but it is contraindicated for persons with human immunodeficiency virus (HIV) infection because it can result in severe disease in this population. In tuberculosis-endemic regions, BCG vaccine is administered soon after birth, before in utero and peripartum HIV infection is excluded. We therefore assessed the immunogenicity of BCG vaccine in HIV-exposed infants who received BCG at birth or at 8 weeks of age.

METHODS:

HIV-exposed, uninfected infants were randomly assigned to receive BCG vaccination at birth (the early vaccination arm) or 8 weeks of age (the delayed vaccination arm). BCG-specific proliferative and intracellular cytokine responses were assessed in 28 infants per arm at 6, 8, and 14 weeks of life.

RESULTS:

There was no difference in BCG-specific T-cell proliferation between the study arms 6 weeks after vaccination. However, at 14 weeks of age, the frequency of interferon γ-expressing CD4(+) T cells and multifunctional BCG-specific responses in the delayed vaccinated arm were significantly higher than those in the early vaccination arm (P = .021 and P = .011, respectively).

CONCLUSIONS:

The immunogenicity of BCG vaccination in HIV-exposed, uninfected infants is not compromised when delayed until 8 weeks of age and results in robust BCG-specific T-cell responses at 14 weeks of age. These findings support further evaluation of this modified BCG vaccination strategy for HIV-exposed infants.

http://jid.oxfordjournals.org/content/211/3/338.long

Typhoid vaccine

Clin Infect Dis. 2015 Apr 13. pii: civ295. [Epub ahead of print]

Safety and Immunogenicity of a Vi Polysaccharide-Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study.

Mohan VK[1], Varanasi V[1], Singh A[1], Pasetti MF[2], Levine MM[2], Venkatesan R[1], Ella KM[1].

Bharat Biotech International Limited, Hyderabad, Telangana, India.; Centre for Vaccine Development, University of Maryland School of Medicine, Baltimore.

BACKGROUND:

Enteric fever caused by Salmonella Typhi remains a major public health problem in developing countries. Typbar-TCV is a single-dose typhoid Vi polysaccharide-tetanus toxoid conjugate vaccine for persons ≥6 months of age.

METHODS:

Six hundred fifty-four healthy subjects aged 2-45 years enrolled in a double-blind, randomized controlled trial (RCT) received a single dose of Typbar-TCV or comparator "Vi polysaccharide" (Typbar), and 327 healthy subjects aged 6-23 months received a single dose of Typbar-TCV in an open-label trial (OLT); both received single- or multidose presentations from different lots. After 2 years, subsets in each group received a booster dose. The primary objective included analysis of geometric mean titer (GMTs) and 4-fold rise of anti-Vi serum immunoglobulin G (IgG) enzyme-linked immunosorbent assay titers over baseline (seroconversion [SCN]) 42 days after immunization.

RESULTS:

Typbar-TCV recipients in the RCT attained higher anti-Vi IgG GMTs 42 days after immunization (SCN, 97%; GMT, 1293 [95% confidence interval {CI}, 1153-1449]) than recipients of Typbar (SCN, 93%; GMT, 411 [95% CI, 359-471]) (P < .001). Typbar-TCV was highly immunogenic in the OLT (SCN, 98%; GMT, 1937 [95% CI, 1785-2103]). Two years after vaccination, anti-Vi titers remained higher in Typbar-TCV subjects (GMT, 82 [95% CI, 73-92]); and exhibited higher avidity (geometric mean avidity index [GMAI], 60%) than in Typbar recipients (GMT, 46 [95% CI, 40-53]; GMAI 46%) in the RCT (P < .001). OLT Typbar-TCV recipients achieved GMT of 48 (95% CI, 42-55) and GMAI of 57%. Typbar-TCV induced multiple IgG subclasses and strong booster responses in all ages. No serious vaccine-attributable adverse events were observed.

CONCLUSIONS:

Single-dose Typbar-TCV is well tolerated and induces robust and long-lasting serum anti-Vi IgG across age groups.

Varicella vaccine

Hum Vaccin Immunother. 2015;11(2):443-9. doi: 10.1080/21645515.2014.1004031.

Safety and immunogenicity of single dose live attenuated varicella vaccine (VR 795 Oka strain) in healthy Indian children: a randomized controlled study.

Mitra M[1], Faridi M, Ghosh A, Shah N, Shah R, Chaterjee S, Narang M, Bhattacharya N, Bhat G, Choudhury H, Kadhe G, Mane A, Roy S.

a Institute of Child Health ; Kolkata , India.

Abstract

Varicella, an acute viral systemic infection that may cause lifelong latent infection with the potential for causing clinical reactivation, may be prevented by immunization. The present study was an open label, randomized, controlled, phase III, multicentre trial, conducted to evaluate

and compare the safety, tolerability and immunogenicity of a freeze dried live attenuated Oka strain Varicella Vaccine (VR 795 Oka strain) with Varilrix (Oka-RIT strain) in children. A total of 268 healthy Indian children aged 12 months to 12 y with baseline VZV IgG antibody (<100 mIU/ mL) were enrolled, and 256 children completed the study. The extent of rise of VZV IgG antibody titer assessed as 3-fold and 4-fold rise from baseline was found to be significantly higher (89.1% and 85.2%) in the test group as compared to control group (73.4% and 61.7%). The post-vaccination GMT of the test group was significantly higher (112.5 mIU/mL) as compared with the control group (67.8 mIU/mL) ($P < 0.001$). The seroconversion rate considering the 5 gp ELISA units/ml equivalent to 10mIU/ml were similar in the control (96.5%) and the test (98.3%) groups. The adverse events were not different in the control and test groups ($P > 0.05$). The test live attenuated vaccine was found to be highly immunogenic, safe and comparable to Varilrix used in control arm.

http://www.tandfonline.com/doi/full/10.1080/21645515.2014.1004031#abstract

Vitamin A

(See also: Maternal health - nutrition and micronutrient supplementation; HIV - prevention of mother to child transmission; Helminths)

Lancet. 2015 Apr 4;385(9975):1333-42. doi: 10.1016/S0140-6736(14)60891-6. Epub 2014 Dec 11.

Efficacy of early neonatal supplementation with vitamin A to reduce mortality in infancy in Haryana, India (Neovita): a randomised, double-blind, placebo-controlled trial.

Mazumder S[1], Taneja S[1], Bhatia K[1], Yoshida S[2], Kaur J[1], Dube B[1], Toteja GS[3], Bahl R[2], Fontaine O[2], Martines J[4], Bhandari N[5]; Neovita India Study Group.

Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.; Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland.; Centre for Promotion of Nutrition Research and Training, Indian Council of Medical Research, New Delhi, India.; Centre for Intervention Science in Maternal and Child Health (CISMAC), Centre for International Health, University of Bergen, Bergen, Norway; Centre for Health Research and Development, Society for Applied Studies, New Delhi, India.

BACKGROUND:

Vitamin A supplementation in children aged 6 months to 5 years has been shown to reduce mortality. The efficacy of neonatal supplementation with vitamin A to reduce mortality in the first 6 months of life is plausible but not established. We aimed to assess the efficacy of neonatal oral supplementation with vitamin A to reduce mortality between supplementation and 6 months of age.

METHODS:

We undertook an individually randomised, double-blind, placebo-controlled trial in Haryana, India. We identified pregnant women through a surveillance programme undertaken every 3 months of all female residents in two districts of Haryana, India, aged 15-49 years, and screened

every identified livebirth. Eligible participants were neonates whose parents consented to participate, were likely to stay in the study area until at least 6 months of age, and were able to feed orally at the time of enrolment. Participants were randomly assigned to receive oral capsules containing vitamin A (retinol palmitate 50,000 IU plus vitamin E 9·5-12·6 IU) or placebo (vitamin E 9·5-12·6 IU) within 72 h of birth. Randomisation was in blocks of 20 according to a randomisation list prepared by a statistician not otherwise involved with the trial. Investigators, participants' families, and the data analysis team were masked to treatment allocation. The primary outcome was mortality between supplementation and 6 months of age. Analysis included all participants assigned to study groups. This trial is registered with ClinicalTrials.gov, number NCT01138449, and the Indian Council of Medical Research Clinical Trial Registry, number CTRI/2010/091/000220.

FINDINGS:

Between June 24, 2010, and July 1, 2012 we screened 47,777 neonates and randomly assigned 44,984 to receive vitamin A (22,493) or placebo (22,491). Between supplementation and 6 months of age, 656 infants died in the vitamin A group compared with 726 in the placebo group (29·2 per 1000 vs 32·3 per 1000; difference -3·1 per 1000, 95% CI -6·3 to 0·1; risk ratio 0·90, 95% CI 0·81 to 1·00). We noted no significant interactions between the intervention effect and sex on mortality at 6 months (p=0·409). Supplementation with 50,000 IU vitamin A within the first 72 h of life was generally safe and well tolerated, with the exception of a small excess risk of transient bulging fontanelle (205 cases in the vitamin A group confirmed by physician vs 80 cases in the placebo group, risk ratio 2·56 [95% CI 1·98-3·32]).

INTERPRETATION:

The findings of this study, done in a population in which vitamin A deficiency is a moderate public health problem, are consistent with a modest reduction in mortality between supplementation and 6 months of age. These findings must be viewed together with similar trials in other populations to enable determination of appropriate public health policy.

Lancet. 2015 Apr 4;385(9975):1315-23. doi: 10.1016/S0140-6736(14)60880-1. Epub 2014 Dec 11.

Effect of early neonatal vitamin A supplementation on mortality during infancy in Ghana (Neovita): a randomised, double-blind, placebo-controlled trial.

Edmond KM[1], Newton S[2], Shannon C[3], O'Leary M[3], Hurt L[4], Thomas G[5], Amenga-Etego S[5], Tawiah-Agyemang C[5], Gram L[3], Hurt CN[4], Bahl R[6], Owusu-Agyei S[7], Kirkwood BR[3].

School of Paediatrics and Health, University of Western Australia, Perth, WA, Australia. ; Kintampo Health Research Centre, Kintampo, Ghana; London School of Hygiene and Tropical Medicine, London, UK.; London School of Hygiene and Tropical Medicine, London, UK.; School of Medicine, Cardiff University, Cardiff, UK.; Kintampo Health Research Centre, Kintampo, Ghana.; World Health Organization, Geneva, Switzerland.; London School of Hygiene and Tropical Medicine, London, UK; Kintampo Health Research Centre, Kintampo, Ghana.

BACKGROUND:

Results of randomised controlled trials of newborn (age 1-3 days) vitamin A supplementation have been inconclusive. The WHO is coordinating three large randomised trials in Ghana, India, and Tanzania (Neovita trials). We present the findings of the Neovita trial in Ghana.

METHODS:

This study was a population-based, individually randomised, double-blind, placebo-controlled trial in the Brong Ahafo region of Ghana. The trial participants were infants aged at least 2 h, identified at home or facilities on the day of birth or in the next 2 days, able to feed orally, and likely to stay in the study area for at least 6 months. They were randomly assigned (ratio 1:1) to receive either one oral dose of vitamin A (50,000 IU) or placebo immediately after recruitment. The research team and parents of the infants were masked to treatment assignment. Follow-up home visits were undertaken every 4 weeks, when data were recorded for deaths, facility use, and care seeking. The primary outcome was post-supplementation mortality to 6 months of age. Analysis was by intention to treat. Potential adverse events were recorded at 1 and 3 days after supplementation. This trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR)CTRN12610000582055.

FINDINGS:

We assessed 26,414 livebirths for eligibility between Aug 16, 2010, and Nov 7, 2011. We recruited 22,955 newborn infants, with 11,474 randomly assigned to receive vitamin A and 11,481 to receive placebo. Loss to follow-up was low with vital status at 6 months of age reported for 22,698 (98·9%) infants. We recorded 278 post-supplementation deaths to 6 months of age in the vitamin A group (mortality risk 24·5 in 1000 supplemented infants) and 248 deaths in the placebo group (mortality risk 21·8 per 1000 supplemented infants), relative risk (RR) 1·12 (95% CI 0·95-1·33; p=0·183) and risk difference (RD) 2·66 (95% CI -1·25 to 6·57; p=0·18). Adverse events within 3 days of supplementation did not differ by trial group. 122 infants died in the first 3 days after supplementation; 70 (0·6%) in the vitamin A and 52 (0·5%) in the placebo group (risk ratio [RR] 1·35, 95% CI 0·94-1·93, p=0·102). 53 infants were reported to have a bulging fontanelle; 32 (0·3%) in the vitamin A group and 21 (0·2%) in the placebo group (RR 1·53, 0·88-2·62, p=0·130).

INTERPRETATION:

The results of this trial do not support inclusion of newborn vitamin A supplementation as a child survival strategy in Ghana.

Lancet. 2015 Apr 4;385(9975):1324-32. doi: 10.1016/S0140-6736(14)61731-1. Epub 2014 Dec 11.

Effect of neonatal vitamin A supplementation on mortality in infants in Tanzania (Neovita): a randomised, double-blind, placebo-controlled trial.

Masanja H[1], Smith ER[2], Muhihi A[3], Briegleb C[2], Mshamu S[3], Ruben J[2], Noor RA[4], Khudyakov P[2], Yoshida S[5], Martines J[5], Bahl R[5], Fawzi WW[2]; Neovita Tanzania Study Group.

Ifakara Health Institute, Dar es Salaam, Tanzania.; Harvard School of Public Health, Department of Global Health and Population, Boston, MA, USA.; African Academy for Public Health, Dar es Salaam, Tanzania; Harvard School of Public Health, Department of Global Health and Population, Boston, MA, USA; African Academy for Public Health, Dar es Salaam, Tanzania. ; Department of Maternal, Newborn, Child and Adolescent Health, WHO, Geneva, Switzerland.

BACKGROUND:

Supplementation of vitamin A in children aged 6-59 months improves child survival and is implemented as global policy. Studies of the efficacy of supplementation of infants in the

neonatal period have inconsistent results. We aimed to assess the efficacy of oral supplementation with vitamin A given to infants in the first 3 days of life to reduce mortality between supplementation and 180 days (6 months).

METHODS:

We did an individually randomised, double-blind, placebo-controlled trial of infants born in the Morogoro and Dar es Salaam regions of Tanzania. Women were identified during antenatal clinic visits or in the labour wards of public health facilities in Dar es Salaam. In Kilombero, Ulanga, and Kilosa districts, women were seen at home as part of the health and demographic surveillance system. Newborn infants were eligible for randomisation if they were able to feed orally and if the family intended to stay in the study area for at least 6 months. We randomly assigned infants to receive one dose of 50,000 IU of vitamin A or placebo in the first 3 days after birth. Infants were randomly assigned in blocks of 20, and investigators, participants' families, and data analysis teams were masked to treatment assignment. We assessed infants on day 1 and day 3 after dosing, as well as at 1, 3, 6, and 12 months after birth. The primary endpoint was mortality at 6 months, assessed by field interviews. The primary analysis included only children who were not lost to follow-up. This trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), number ACTRN12610000636055.

FINDINGS:

Between Aug 26, 2010, and March 3, 2013, 31,999 newborn babies were randomly assigned to receive vitamin A (n=15,995) or placebo (n=16,004; 15,428 and 15,464 included in analysis of mortality at 6 months, respectively). We did not find any evidence for a beneficial effect of vitamin A supplementation on mortality in infants at 6 months (26 deaths per 1000 livebirths in vitamin A vs 24 deaths per 1000 livebirths in placebo group; risk ratio 1·10, 95% CI 0·95-1·26; p=0·193). There was no evidence of a differential effect for vitamin A supplementation on mortality by sex; risk ratio for mortality at 6 months for boys was 1·08 (0·90-1·29) and for girls was 1·12 (0·91-1·39). There was also no evidence of adverse effects of supplementation within 3 days of dosing.

INTERPRETATION:

Neonatal vitamin A supplementation did not result in any immediate adverse events, but had no beneficial effect on survival in infants in Tanzania. These results strengthen the evidence against a global policy recommendation for neonatal vitamin A supplementation.

Vaccine. 2014 Sep 22;32(42):5468-74. doi: 10.1016/j.vaccine.2014.07.090. Epub 2014 Aug 13.

Interaction between neonatal vitamin A supplementation and timing of measles vaccination: a retrospective analysis of three randomized trials from Guinea-Bissau.

Benn CS[1], Martins CL[2], Fisker AB[3], Diness BR[3], Garly ML[3], Balde I[2], Rodrigues A[2], Whittle H[4], Aaby P[5].

Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, , Institute of Clinical Research, University of Southern Denmark/Odense University Hospital, Denmark. ; Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau. Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project,Copenhagen S, Denmark.; The London School of Hygiene and Tropical Medicine, Keppel Street, London, UK.; Research Center for Vitamins

and Vaccines (CVIVA), Bandim Health Project,, Denmark; Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau.

BACKGROUND:

In Guinea-Bissau we conducted three trials of neonatal vitamin A supplementation (NVAS) from 2002 to 2008. None of the trials found a beneficial effect on mortality. From 2003 to 2007, an early measles vaccine (MV) trial was ongoing, randomizing children 1:2 to early MV at 4.5 months or no early MV, in addition to the usual MV at 9 months. We have previously found interactions between vitamin A and vaccines.

OBJECTIVE:

We investigated whether there were interactions between NVAS and early MV.

DESIGN:

We compared the mortality of NVAS and placebo recipients: first, from 4.5 to 8 months for children randomized to early MV or no early MV; and second, from 9 to 17 months in children who had received two MV or one MV. Mortality rates (MR) were compared in Cox models producing mortality rate ratios (MRR).

RESULTS:

A total of 5141 children were randomized to NVAS (N=3015) or placebo (N=2126) and were later randomized to early MV (N=1700) or no early MV (N=3441). Between 4.5 and 8 months, NVAS compared with placebo was associated with higher mortality in early MV recipients (MR=30 versus MR=0, p=0.01), but not in children who did not receive early MV (p for interaction between NVAS and early MV=0.03). From 9 to 17 months NVAS was not associated with mortality. Overall, from 4.5 to 17 months NVAS was associated with increased mortality in early MV recipients (Mortality rate ratio=5.39 (95% confidence interval: 1.62, 17.99)).

CONCLUSIONS:

These observations indicate that NVAS may interact with vaccines given several months later. This may have implications for the planning of future child intervention programs.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4180001/

BMC Pediatr. 2014 Aug 28;14:214. doi: 10.1186/1471-2431-14-214.

Neonatal vitamin A supplementation associated with a cluster of deaths and poor early growth in a randomised trial among low-birth-weight boys of vitamin A versus oral polio vaccine at birth.

Lund N[1], Biering-Sørensen S, Andersen A, Monteiro I, Camala L, Jørgensen MJ, Aaby P, Benn CS.

Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark.

BACKGROUND:

The effect of oral polio vaccine administered already at birth (OPV0) on child survival was not examined before being recommended in 1985. Observational data suggested that OPV0 was harmful for boys, and trials have shown that neonatal vitamin A supplementation (NVAS) at birth may be beneficial for boys. We set out to test this research question in a randomised trial.

METHODS:

The trial was carried out at the Bandim Health Project, Guinea-Bissau. We planned to enrol 900 low-birth weight (LBW) boys in a randomised trial to investigate whether NVAS instead of OPV0 could lower infant mortality for LBW boys. At birth, the children were randomised to OPV (usual treatment) or VAS (intervention treatment) and followed for 6 months for growth and 12 months for survival. Hazard Ratios (HR) for mortality were calculated using Cox regression. We compared the individual anthropometry measurements to the 2006 WHO growth reference. We compared differences in z-scores by linear regression. Relative risks (RR) of being stunted or underweight were calculated in Poisson regression models with robust standard errors.

RESULTS:

In the rainy season we detected a cluster of deaths in the VAS group and the trial was halted immediately with 232 boys enrolled. The VAS group had significantly higher mortality than the OPV0 group in the rainy season (HR: 9.91 (1.23 - 80)). All deaths had had contact with the neonatal nursery; of seven VAS boys enrolled during one week in September, six died within two months of age, whereas only one died among the six boys receiving OPV (p = 0.05). Growth (weight and arm-circumference) in the VAS group was significantly worse until age 3 months.

CONCLUSION:

VAS at birth instead of OPV was not beneficial for the LBW boys in this study. With the premature closure of the trial it was not possible to answer the research question. However, the results of this study call for extra caution when testing the effect of NVAS in the future.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4236664/pdf/1471-2431-14-214.pdf

J Nutr. 2014 Sep;144(9):1474-9. doi: 10.3945/jn.114.192674. Epub 2014 Jul 2.

Two different doses of supplemental vitamin A did not affect mortality of normal-birth-weight neonates in Guinea-Bissau in a randomized controlled trial.

Benn CS[1], Diness BR[2], Balde I[3], Rodrigues A[3], Lausch KR[2], Martins CL[3], Fisker AB[2], Aaby P[4].

Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark; Odense Patient data Explorative Network, Institute of Clinical Research, University of Southern Denmark/Odense University Hospital, Odense, Denmark; Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark;; Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau; Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark; Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau; and.

Abstract

Whether neonatal vitamin A supplementation (NVAS) should be policy in areas with vitamin A deficiency is debated. We observed that a smaller dose of vitamin A may decrease mortality more than a larger dose and conducted a randomized, double-blind, placebo-controlled trial in Guinea-Bissau with the primary aim of comparing the effect of 50,000 with 25,000 IU neonatal vitamin A on infant mortality. The secondary aim was to study the effect of NVAS vs. placebo, including a combined analysis of NVAS trials. Between 2004 and 2007, normal-birth-weight neonates were randomly assigned in a 1:1:1 ratio to be administered 2 different doses of vitamin A (50,000 or 25,000 IU) or placebo. Infant mortality rates (MRs) were compared in Cox models providing MR ratios (MRRs). Among 6048 children enrolled, there were 160 deaths in 4125 person-years (MR = 39/1000). There was no difference in mortality between the 2 dosage groups: the MRR for 25,000 vs. 50,000 IU was 0.96 (95% CI: 0.67, 1.38). Neither dose of NVAS was associated with lower mortality than placebo (MRR = 1.28; 95% CI: 0.91, 1.81). In a combined analysis of the present trial and 2 previous NVAS trials in Guinea-Bissau, the effect of receiving NVAS (any dose) vs. placebo was 1.13 (95% CI: 0.94, 1.36) and differed significantly (P = 0.01) between boys (0.80; 95% CI: 0.58, 1.09) and girls (1.35; 95% CI: 1.04, 1.75). We could not confirm that a smaller dose of neonatal vitamin A reduces mortality more than a larger dose. We confirmed 2 other trials in Guinea-Bissau that showed no beneficial effect of NVAS.

Pediatrics. 2014 Sep;134(3):e739-48. doi: 10.1542/peds.2014-0550.

High-dose vitamin A with vaccination after 6 months of age: a randomized trial.

Fisker AB[1], Bale C[2], Rodrigues A[2], Balde I[2], Fernandes M[2], Jørgensen MJ[3], Danneskiold-Samsøe N[3], Hornshøj L[2], Rasmussen J[2], Christensen ED[2], Bibby BM[4], Aaby P[5], Benn CS[6].

Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau; Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark; Department of Biostatistics, Institute of Public Health, University of Aarhus, Aarhus, Denmark; Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau; Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark; Institute of Clinical Research, University of Southern Denmark/Odense University Hospital, Odense, Denmark.

BACKGROUND:

The World Health Organization recommends vitamin A supplementation (VAS) at routine vaccination contacts after 6 months of age based on the assumption that it reduces mortality by 24%. The policy has never been evaluated in randomized controlled trials for its effect on overall mortality. We conducted a randomized double-blind trial to evaluate the effect of VAS with vaccines.

METHODS:

We randomized children aged 6 to 23 months 1:1 to VAS (100000 IU if aged 6-11 months, 200000 IU if aged 12-23 months) or placebo at vaccination contacts in Guinea-Bissau. Mortality rates were compared in Cox proportional-hazards models overall, and by gender and vaccine.

RESULTS:

Between August 2007 and November 2010, 7587 children were enrolled. Within 6 months of follow-up 80 nonaccident deaths occurred (VAS: 38; placebo: 42). The mortality rate ratio (MRR) comparing VAS versus placebo recipients was 0.91 (95% confidence interval 0.59-1.41) and differed significantly between boys (MRR 1.92 [0.98-3.75]) and girls (MRR 0.45 [0.24-0.87]) (P = .003 for interaction between VAS and gender). At enrollment, 42% (3161/7587) received live measles vaccine, 29% (2154/7587) received inactivated diphtheria-tetanus-pertussis-containing vaccines, and 21% (1610/7587) received both live and inactivated vaccines. The effect of VAS did not differ by vaccine group.

CONCLUSIONS:

This is the first randomized controlled trial to assess the effect of the policy on overall mortality. VAS had no overall effect, but the effect differed significantly by gender. More trials to ensure an optimal evidence-based vitamin A policy are warranted.

Am J Clin Nutr. 2014 Dec;100(6):1541-50. doi: 10.3945/ajcn.114.087379. Epub 2014 Oct 8.

Biofortified orange maize is as efficacious as a vitamin A supplement in Zambian children even in the presence of high liver reserves of vitamin A: a community-based, randomized placebo-controlled trial.

Gannon B[1], Kaliwile C[1], Arscott SA[1], Schmaelzle S[1], Chileshe J[1], Kalungwana N[1], Mosonda M[1], Pixley K[1], Masi C[1], Tanumihardjo SA[1].

From the Interdepartmental Graduate Program in Nutritional Sciences, University of Wisconsin-Madison, Madison, WI (BG, SAA, SS, and SAT); National Food and Nutrition Commission of Zambia, Lusaka, Zambia (CK, MM, and CM); Tropical Diseases Research Centre, Ndola, Zambia (JC and NK); and International Maize and Wheat Improvement Center, Texcoco, Mexico (KP).

BACKGROUND:

Biofortification is a strategy to relieve vitamin A (VA) deficiency. Biofortified maize contains enhanced provitamin A concentrations and has been bioefficacious in animal and small human studies.

OBJECTIVE:

The study sought to determine changes in total body reserves (TBRs) of vitamin A with consumption of biofortified maize.

DESIGN:

A randomized, placebo-controlled biofortified maize efficacy trial was conducted in 140 rural Zambian children. The paired (13)C-retinol isotope dilution test, a sensitive biomarker for VA status, was used to measure TBRs before and after a 90-d intervention. Treatments were white maize with placebo oil (VA-), orange maize with placebo (orange), and white maize with VA in oil [400 μg retinol activity equivalents (RAEs) in 214 μL daily] (VA+).

RESULTS:

In total, 133 children completed the trial and were analyzed for TBRs (n = 44 or 45/group). Change in TBR residuals were not normally distributed (P < 0.0001); median changes (95% CI) were as follows: VA-, 13 (-19, 44) μmol; orange, 84 (21, 146) μmol; and VA+, 98 (24, 171) μmol. Nonparametric analysis showed no statistical difference between VA+ and orange (P = 0.34); both were higher than VA- (P = 0.0034). Median (95% CI) calculated liver reserves at baseline were 1.04 (0.97, 1.12) μmol/g liver, with 59% >1 μmol/g, the subtoxicity cutoff; none were <0.1 μmol/g, the deficiency cutoff. The calculated bioconversion factor was 10.4 μg β-carotene equivalents/1 μg retinol by using the middle 3 quintiles of change in TBRs from each group. Serum retinol did not change in response to intervention (P = 0.16) but was reduced with elevated C-reactive protein (P = 0.0029) and α-1-acid glycoprotein (P = 0.0023) at baseline.

CONCLUSIONS:

β-Carotene from maize was efficacious when consumed as a staple food in this population and could avoid the potential for hypervitaminosis A that was observed with the use of preformed VA from supplementation and fortification. Use of more sensitive methods other than serum retinol alone, such as isotope dilution, is required to accurately assess VA status, evaluate interventions, and investigate the interaction of VA status and infection.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232019/pdf/ajcn10061541.pdf

Vitamin D

(see also Tuberculosis)

J Nutr. 2015 Jan;145(1):121-7. doi: 10.3945/jn.114.201566. Epub 2014 Nov 12.

Vitamin D status is associated with mortality, morbidity, and growth failure among a prospective cohort of HIV-infected and HIV-exposed Tanzanian infants.

Sudfeld CR[1], Duggan C[2], Aboud S[3], Kupka R[4], Manji KP[5], Kisenge R[5], Fawzi WW[6].

Departments of Global Health and Population, ; Nutrition, and Division of Gastroenterology and Nutrition, Boston Children's Hospital and Harvard Medical School, Boston, MA; Departments of.; Microbiology and Immunology; Nutrition, and UNICEF Headquarters, New York, NY.; Paediatrics and Child Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; Departments of Global Health and Population, Nutrition, and Epidemiology, Harvard School of Public Health, Boston, MA;

BACKGROUND:

Vitamin D is a potent immunomodulator, but its impact on morbidity and mortality among infants remains unclear.

OBJECTIVE:

The objective of the study was to prospectively assess the association of vitamin D status with mortality, morbidity, and growth during the first 2 y of life.

METHODS:

A prospective cohort of 253 HIV-infected and 948 HIV-exposed Tanzanian infants enrolled in a randomized trial of multivitamins (not including vitamin D) was studied. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured at 5-7 wk of age and infants were followed at monthly clinic visits until 24 mo. Physicians performed a clinical exam every 3 mo or when an illness was noted.

RESULTS:

Serum 25(OH)D concentrations were (means ± SDs) 18.6 ± 10.3 ng/mL and 18.1 ± 9.2 ng/mL for HIV-infected and HIV-exposed infants, respectively. Unexpectedly, serum 25(OH)D concentrations ≥30 ng/mL were significantly associated with higher mortality as compared to the 20-29.9 ng/mL reference for HIV-infected (HR: 2.47; 95% CI: 1.13, 5.44; P = 0.02) and HIV-exposed (HR: 4.00; 95% CI: 1.67, 9.58; P < 0.01) infants after multivariate adjustment. We found no statistically significant association between 25(OH)D concentrations <10 ng/mL and mortality for HIV-infected (HR: 1.43; 95% CI: 0.74, 2.78; P = 0.29) and HIV-exposed (HR: 1.56; 95% CI: 0.60, 4.03; P = 0.36) infants. Among HIV-exposed infants, 25(OH)D concentrations ≥30 ng/mL were significantly associated with clinical [incidence ratio rate (IRR): 1.34; 95% CI: 1.06,1.70; P = 0.02] and confirmed (IRR: 1.71; 95% CI: 1.71; 1.15, 2.54; P < 0.01) malaria diagnoses, whereas concentrations of <10 ng/mL were associated with oral candidiasis (IRR: 1.47; 95% CI: 1.00-2.15; P = 0.046) and wasting (HR: 1.71; 95% CI: 1.20, 2.43; P < 0.01).

CONCLUSION:

The observational design of this study does not allow for causal interpretation; however, the results indicate a strong need for additional studies of vitamin D among HIV-infected and -exposed children, particularly in malaria-endemic settings.

J Allergy Clin Immunol. 2014 Oct;134(4):831-835.e1. doi: 10.1016/j.jaci.2014.08.002.

Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children.

Camargo CA Jr[1], Ganmaa D[2], Sidbury R[3], Erdenedelger Kh[4], Radnaakhand N[5], Khandsuren B[4].

Massachusetts General Hospital, Harvard Medical School, and Harvard School of Public Health, Boston, Mass.; Massachusetts General Hospital, Harvard Medical School, and Harvard School of Public Health, Boston, Mass; Health Sciences University of Mongolia, Ulaanbaatar, Mongolia.; Seattle Children's Hospital, Seattle, Wash.; Health Sciences University of Mongolia, Ulaanbaatar, Mongolia; National Dermatology Center, Ulaanbaatar, Mongolia.; Health Sciences University of Mongolia, Ulaanbaatar, Mongolia.

BACKGROUND:

Epidemiologic and preclinical data, and a small randomized trial in Boston, suggest that vitamin D supplementation may improve winter-related atopic dermatitis (AD).

OBJECTIVE:

To determine the effect of vitamin D supplementation on winter-related AD.

METHODS:

We performed a randomized, double-blind, placebo-controlled trial of Mongolian children with winter-related AD. Baseline eligibility included age 2 to 17 years, AD score 10 to 72 using the Eczema Area and Severity Index (EASI), and winter-related AD (eg, history of AD worsening during the fall-to-winter transition). Subjects were enrolled in Ulaanbaatar during winter and randomly assigned to oral cholecalciferol (1000 IU/day) versus placebo for 1 month. All children and parents received emollient and patient education about AD and basic skin care. The main outcomes were changes in EASI score and in Investigator's Global Assessment.

RESULTS:

The 107 enrolled children had a mean age of 9 years (SD 5), and 59% were male. Their median age of AD onset was 3 months (interquartile range 2 months to 1 year) and mean EASI score at baseline 21 (SD 9). One-month follow-up data were available for 104 (97%) children. Compared with placebo, vitamin D supplementation for 1 month produced a clinically and statistically significant improvement in EASI score (adjusted mean change: -6.5 vs -3.3, respectively; P = .04). Moreover, change in Investigator's Global Assessment favored vitamin D over placebo (P = .03). There were no adverse effects in either group.

CONCLUSION:

Vitamin D supplementation improved winter-related AD among Mongolian children, a population likely to have vitamin D deficiency in winter.

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

J Nutr. 2014 Aug;144(8):1298-305. doi: 10.3945/jn.113.189365. Epub 2014 May 21.

Zinc supplementation sustained normative neurodevelopment in a randomized, controlled trial of Peruvian infants aged 6-18 months.

Colombo J[1], Zavaleta N[2], Kannass KN[3], Lazarte F[2], Albornoz C[2], Kapa LL[4], Caulfield LE[5].

Schiefelbusch Institute for Life Span Studies and Department of Psychology, University of Kansas, Lawrence, ;Nutritional Research Institute, Lima, Peru.; Department of Psychology, Loyola University of Chicago, Chicago, IL.; Department of Speech, Language, and Hearing Sciences, University of Arizona, Tucson, AZ; Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD.

Abstract

A double-blind, randomized clinical trial was conducted to determine the effects of prevention of zinc deficiency on cognitive and sensorimotor development during infancy. At 6 mo of age, infants were randomly assigned to be administered a daily liquid supplement containing 10 mg/d of zinc (zinc sulfate), 10 mg/d of iron (ferrous sulfate), and 0.5 mg/d of copper (copper

oxide), or an identical daily liquid supplement containing only 10 mg/d of iron and 0.5 mg/d of copper. Various controls were implemented to ensure adherence to the supplement protocol. A battery of developmental assessments was administered from 6 to 18 mo of age that included a visual habituation/recognition memory task augmented with heart rate at 6, 9, and 12 mo of age; the Bayley Scales of Infant Development, 2nd edition (BSID2) at 6, 12, and 18 mo; the A-not-B error task at 9 and 12 mo; and free-play attention tasks at 12 and 18 mo. Only infants supplemented with zinc had the normative decline in look duration from 6 to 12 mo during habituation and a normative decline in shifting between objects on free-play multiple-object attention tasks from 12 to 18 mo of age. The 2 groups did not differ on any of the psychophysiologic indices, the BSID2, or the A-not-B error task. The findings are consistent with zinc supplementation supporting a profile of normative information processing and active attentional profiles during the first 2 y of life.

Indian Pediatr. 2014 Oct;51(10):780-4.

Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial.

Malik A[1], Taneja DK, Devasenapathy N, Rajeshwari K.

Departments of Community Medicine and *Pediatrics, Maulana Azad Medical College, New Delhi, India; and #Indian Institute of Public Health, Gurgaon, Haryana, India. Correspondence Ministry of Health and Family Welfare, Government of India, Nirman Bhawan, New Delhi,India.

OBJECTIVE:

To study the effect of 2 weeks of prophylactic zinc supplementation on incidence and duration of acute respiratory infections.

DESIGN:

Randomized double blind controlled trial.

SETTING:

Community based; urban resettlement area in North-East Delhi, India.

PARTICIPANTS:

272 children aged 6-11 months with acute respiratory infections. Children receiving zinc supplement within the past 3 months, severely malnourished, immuno-deficient, on steroid therapy, with severe illness requiring hospitalization, or children of families likely to migrate from the study area were excluded.

INTERVENTION:

Placebo (syrup base) or zinc (20 mg/5 mL elemental zinc as zinc sulfate) orally given for a period of 2 weeks.

MAIN OUTCOME MEASURE(S):

Incidence, type and duration of acute respiratory infections, and adverse effects.

RESULTS:

No effect on incidence of acute respiratory infections was noted. A decrease of 15% (0.78-0.94) in days and 12% (0.78-0.94) in duration of episode in acute respiratory infections was observed. Incidence of acute lower respiratory infections decreased by 62% (0.26-0.36) and the effect remained for full five months of follow up. There were no drop outs due to side effects.

CONCLUSIONS:

Prophylactic zinc supplementation for two weeks may reduce the morbidity due to acute lower respiratory infections but not overall rate of acute respiratory infections in infants aged 6-11 months in similar populations.

J Acquir Immune Defic Syndr. 2014 Aug 1;66(4):386-92. doi: 10.1097/QAI.0000000000000191.

Immunologic effect of zinc supplementation in HIV-infected children receiving highly active antiretroviral therapy: a randomized, double-blind, placebo-controlled trial.

Lodha R[1], Shah N, Mohari N, Mukherjee A, Vajpayee M, Singh R, Singla M, Saini S, Bhatnagar S, Kabra SK.

Departments of *Pediatrics; and †Microbiology, All India Institute of Medical Sciences, New Delhi, India.

BACKGROUND:

We conducted this study to assess the immunologic effect of daily 20 mg zinc supplementation for 24 weeks in HIV-infected children older than 6 months receiving highly active antiretroviral therapy (ART).

METHODS:

Fifty-two HIV-infected children older than 6 months in whom ART was initiated were randomized to receive either 20 mg of zinc or placebo for a period of 24 weeks. Children underwent clinical examination, anthropometry, and laboratory evaluations: CD4% and count, viral load, and serum zinc level at baseline, 12 weeks, and 24 weeks. The primary outcome evaluated was CD4% value at the end of 12 and 24 weeks of study intervention in the enrolled children.

RESULTS:

Of 52 children enrolled, 49 completed the study. The median CD4% value rose from 10% to 23% at 12 weeks and to 24.5% at 24 weeks in the zinc group, whereas in the placebo group, the value rose from 11% to 20% at 12 weeks and to 22% at 24 weeks (P = 0.188 for comparison between the zinc and the placebo group at 12 wk and P = 0.3 for comparison at 24 wk). The median (interquartile range) log reductions in the viral load at 12 weeks in the 2 arms were similar at 12 (P = 0.84) and 24 weeks (P = 0.43).

CONCLUSIONS:

Supplementation of 20 mg zinc daily for 24 weeks did not have any statistically significant effect on the increase in CD4%, decrease in viral load, anthropometric indices, and morbidity profile in HIV-infected children started on ART.