RANDOMISED TRIALS IN CHILD AND ADOLESCENT HEALTH IN DEVELOPING COUNTRIES

19th Edition
July 2021-June 2022

Please send suggestions about this booklet to:

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Introduction

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

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

This year I used a simpler search strategy, that was more specific to avoid wading through thousands of studies, but possibly less sensitive. That is why the number of trials identified in 2022 is less than in most of the last few years, but the content is more focused on trials that may change global guidelines, policy or practice in low and mioddle-income countres.

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

This year 126 trial publications were identified. These were conducted in countries from all regions of the world. Several trials from 2021-22 will lead to significant changes in child health recommendations.

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

Please feel free to distribute this booklet to your colleagues. The previous editions (2002-2020) are available at: https://pngpaediatricsociety.org/research-2/

A brief summary of some of the important results from July 2021 to June 2022

- A systematic review of RCTs of fluids and feeding in bronchiolitis, involving over 700 infants showed that nasogastric fluids / feeding, compared with intravenous fluids, showed a 17% relative reduction in the number of intensive care unit admissions and a 19% relative reduction in readmissions to hospital, although neither reached statistical significance.

- Among 2312 children in rural areas of Bangladesh, Ethiopia, India and Malawi with acute lower respiratory infection and chest indrawing but no hypoxaemia (SpO2>90%), 7 days of amoxycillin with close follow up by community-based health care workers was as effective giving the first dose of antibiotics and referral. Failure rates were 5% and 6% respectively, and there were only 2 deaths in each group. This study showed that pulse oximetry was key to safe management of pneumonia in primary health facilities, and community health workers could use oximetry effectively.

- Pulse oximetry was also key to improving quality of care for children with pneumonia in a large scale study involving over 7000 children in Nigeria.

- Among 308 children with severe pneumonia in Bangladesh, IV amoxycillin and gentamicin was as or more effective than IV ampicillin and gentamicin; the amoxycillin group had significantly lower rates of treatment failure and fewer deaths.

- In both Peru and Kenya, digital mobile phone messages sent to adolescents dispelling myths about contraception and sexual and reproductive health, had only a marginal effect on reducing belief in myths. Digital messaging on mobile phones will be insufficient to provide adequate health information or dispel myths.

- In South Africa, peer-to-peer approaches for sharing health information relating to HIV were acceptable and valued by young people. Participants were comfortable sharing sexual health issues they would not share with adults.

- A systematic review of RCTs found that the mental health burden for adolescents living with HIV is high, contributing to low quality of life and challenges with adherence to antiretroviral therapy. Interventions for which there was evidence of benefit in this area included: cognitive behavioural therapy, problem-solving, mindfulness, parenting programs, social protection, and violence prevention.

- A systematic review of oral vs intravenous iron therapy in children with iron deficiency anaemia showed intravenous iron was associated with an increased risk of infection when compared with oral iron or no iron (RR, 1.17; 95% CI, 1.04-1.31. Intravenous iron however improved haemoglobin and reduced the risk of requiring a red blood cell transfusion (RR, 0.93; 95% CI, 0.76-0.89; I2 = 15%) compared with oral iron.

- In a review of 7 RCTs that evaluated antimicrobial stewardship (AMS) programs, education, and clinical decision tools appeared more effective than guidelines alone. AMS interventions resulted in significantly decreased clinical infections and treatment failure and reduced rates of multi-drug resistant organism colonization in hospital wards.

- A large systematic review of RCTs found that unconditional cash transfers may improve some health outcomes, including a reduced risk of having an illness, being food secure, and an improved level of dietary diversity. Unconditional cash transfers may also improve school attendance and reduce the risk of families becoming extremely poor. However cash transfers probably do not improve health service utilisation.

- In 16 Ugandan districts data-driven district management interventions were implemented in an RCT with clinically significant improvements in the treatment of malaria, pneumonia and diarrhoea.

- In Cambodia, a large-scale field trial to reduce dengue vector populations using larvivorous guppy fish in household water containers, mosquito trapping with gravid-ovitraps, solid waste management, breeding-container coverage through community education was successful in reducing entomological indices for dengue. "Where we put little fish in the water there are no mosquitoes"

- In a large multicounty study of 8266 children with acute watery diarrhoea, azithromycin added to standard WHO case management with oral rehydration and zinc did not reduce diarrhoea mortality. The mortality rate was 0.5% and 0.7% in azithromycin and control groups respectively, lower than the researchers expected.

- In a systematic review of studies of children with epilepsy, self-management programmes for educating or counselling affected children and their parents had benefits for the wellbeing of the child: some studies showed reduced seizure frequency or seizure severity, or improved seizure control, however the effects were variable.

- A large systematic review of the effectiveness of anticonvulsants in children showed that in focal onset seizures, current first-line treatment options carbamazepine and lamotrigine, were best in terms of treatment failure and seizure control, but phenytoin and phenobarbitone were also very effective. For people with generalised tonic-clonic seizures (with or without other seizure types), current first-line treatment sodium valproate has the best profile compared to all other treatments, but lamotrigine would be the most suitable alternative.

- In a study of pre- and post-natal exposure to indoor air pollution, the risk for pneumonia and severe pneumonia in infants increased by 10% (relative risk [RR], 1.10; 95% CI, 1.04-1.16) and 15% (RR, 1.15; 95% CI, 1.03-1.28), respectively, per 1-part per million (ppm) increase in average prenatal CO exposure and by 6% (RR, 1.06; 95% CI, 0.99-1.13) per 1-ppm increase in average postnatal CO exposure.

- For first line treatment of HIV in children, the bioavailability of dolutegravir dispersible tablets (both single-drug and fixed-dose combination) was approximately 1.6-fold higher when compared with conventional tablets. In Southern Africa, among over 400 patients with HIV, dolutegravir in combination with nucleoside reverse transcriptase inhibitors was effective, including among those with extensive NRTI resistance. Tenofovir was noninferior to zidovudine as second-line therapy.

- In children with HIV-TB coinfection, earlier initiation of ART (< 4 weeks after commencing TB treatment) did not alter the risk of death compared to initiation of ART after 4 weeks, and earlier may be preferred for logistical and patient preference reasons.

- In a large systematic review of the effect of pre-conception ART vs ART initiation in antenatal care, pre-conception ART was associated with a significantly increased risk of preterm birth (relative risk 1.16; 95% confidence interval [CI] 1.03-1.31) compared with antenatal ART initiation, but no difference in *very* preterm birth, low birthweight, very low birthweight, small for gestational age, very small for gestational age, or neonatal deaths.

- Among children in Ethiopia who were at risk of trachoma, permethrin-impregnated scarves were associated with 35% less contact of the eye, and other parts of the face, by the fly *Musca sorbens*, which can act as a vector for ocular *Chlamydia trachomatis*.

- In a large systematic review of trials of intermittent preventative therapy for malaria, antimalarial drugs known to be effective against the malaria parasite at the time reduced the risk of clinical malaria, anaemia, and hospital admission in infants. However, where there was emerging resistance to antimalarial drugs, such as to sulfadoxine-pyrimethamine (SP), and the efficacy of IPTi with that agent waned over time. Other antimalarials used include amodiaquine-artesunate, SP-artesunate, and dihydroartemisinin-piperaquine.

- In a trial of the WHO Safe Childbirth Checklist in Aceh, Indonesia, with coaching by external trainers (11 visits over 6 months), there were significant improvements in communication of danger signs at admission, measurement of neonatal temperature, newborn feeding checks, and written and verbal communication of danger signs to mothers and birth companions. However many points in the Checklist did not change, suggesting coaching is moderately successful, but not sufficient to improve all aspects of safe birthing practice.

- Mobile phone messaging was trialled to facilitate birth and death registration, child nutrition messages in Cambodia, and decision support in primary care in several countries, all with modest results.

- The use of exchange transfusion in neonatal sepsis was reviewed in a meta-analysis of 14 studies (3 RCTs, 11 controlled observational studies). Exchange transfusion showed a mortality benefit in septic neonates (RR 0.72; CI 0.61-0.86, p = 0.01) and a significant increase in pooled immunological parameters immunoglobulin, complement levels, and neutrophil levels compared to controls. However, the studies were of limited quality, with potential for bias.

- In a small trial in Turkey, intensive support for breast feeding from birth lowered bilirubin levels at 72 hours and reduced the risk of being readmitted with hyperbilirubinemia. And in RCTs in Ethiopia and in Spain, breast feeding education improved early initiation of breast-feeding and exclusive breast-feeding practices to 6 months (PROLACT study in Spain).

- A meta-analysis of RCTs of small-quantity lipid-based nutrient supplements showed decreased stunting (length-for-age z score < -2) by 12% relative reduction, decreased wasting by 14%, reduced low mid-upper arm circumference (MUAC) by 18%, reduced acute malnutrition by 14%, underweight by 13%, and small head size by 9%.

- A meta-analysis of trials of azithromycin mass drug administration clarified the frequency of MDA needed to achieve a trachomatous inflammation-follicular (TF) rate of <5.0% in a population. If baseline prevalence 5-9.9%, a single round of MDA; for districts with baseline between 10-29.9%, annual MDA for 3 to 5 years; and for districts with high level of baseline prevalence >30%, annual MDA did not achieve the TF <5% even after 5 to 7 years, and quarterly MDA was more effective.

- A large meta-analysis of trials of the management of chronic pain in children was conducted, involving: 34 pharmacological trials and 4091 participants; 25 physical therapy trials and 1470 participants; and 63 psychological trials and 5025 participants. Pharmacological, physical, and psychological therapies showed some benefit for reducing pain post-treatment, but only physical and psychological therapies improved physical functioning.

- In non-severe smear negative tuberculosis in 1204 African and Indian children, 4 months (16 weeks) therapy with standard first-line antituberculosis treatment using paediatric fixed-dose combinations (R/H/Z/E) as recommended by the World Health Organization, was not inferior to treatment for 6 months. Short course therapy seems to be effective in non-severe pulmonary TB.

- *** 6861 children 5-17 months of age were randomised to receive (i) chemoprevention with sulfadoxine-pyrimethamine and amodiaquine, (ii) the malaria vaccine: RTS,S/AS01E, or (iii) chemoprevention *plus* RTS,S/AS01E. The protective efficacy of the *combination* as compared with chemoprevention alone was 63% against clinical malaria, 71% against hospital admission with severe malaria according to the World Health Organization definition, and 73% against death from malaria.

- *** A review of routine vitamin A supplementation in Nepal suggested that 3 deaths (range from 1-4 deaths) were averted for every 1000 infants supplemented, and a large meta-analysis of studies of vitamin A from 19 trials showed a 12% observed reduction in the risk of all-cause mortality for vitamin A supplementation compared with control. Nine trials reporting mortality due to diarrhoea showed a 12% overall reduction for vitamin A supplementation. Vitamin A supplementation also reduced the incidence of diarrhoea, measles, and night blindness.

- In a large trial in Papua New Guinea, 3 rounds of mass drug administration (MDA) with azithromycin over 12 months was associated with a significantly lower incidence of yaws ulcers, compared to only one round of MDA plus active treatment of all cases and their contacts.

I have been liberal in what is included as an RCT. Some papers are the reports of sub-studies within an RCT, they may be cohort or background studies rather than the primary results of the completed RCT. This year there is a higher proportion of Cochrane reviews.

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

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

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

Since 2002 there have been **3211 trial publications** summarised in the 19 editions of this book. It is interesting to see the evolution of trials each year. It is encouraging to see the evaluation of the developmental, psychological and mental health effects of interventions. Also encouraging is the increased number of trials that include adolescents; including interventions to reduce violence against adolesents, increase retention in chronic disease programs (such as for HIV), and improve school retention and self-esteem.

Research gaps still exist in many areas, including on appropriate health care models for the management of common chronic childhood conditions, and quality improvement research on how best to provide acute and chronic care for children in remote health care settings.

More support is needed for clinical research capacity in low income countries. The Sustainable Development Goals call us to focus on reducing inequity in order to improve child health, and clinical and public health researchers have a role to play in this.

Trevor Duke
August 2022

Search strategy

((child* or neonate or adolescent) and (World Health Organization)) AND (("2021/06/01"[Date - Publication] : "2022/07/01"[Date - Publication])) AND (Randomised trial)

Acute respiratory infection

(See also: Hygiene and environmental health)

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Parenteral versus enteral fluid therapy for children hospitalised with bronchiolitis

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Abstract

Background: The main focus of treatment for children hospitalised with bronchiolitis is supportive, including oxygen supplementation, respiratory support, and fluid therapy. Up to half of infants hospitalised with bronchiolitis require non-oral fluid therapy due to dehydration or concerns related to the safety of oral feeding. The two main modalities used for non-oral fluid therapy are parenteral (intravenous (IV)) and enteral tube (nasogastric (NG) or orogastric (OG)). However, it is not known which mode is optimal in young children.

Objectives: To systematically review randomised clinical trials (RCTs) of the effectiveness and safety of parenteral and enteral tube fluid therapy for children under two years of age hospitalised with bronchiolitis.

Search methods: We conducted a search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, Web of Science, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform on 8 March 2021. We handsearched conference proceedings, conducted forward and backward searching of citation lists of relevant articles, and contacted experts.

Selection criteria: We included RCTs and quasi-RCTs of children aged up to two years admitted to hospital with a clinical diagnosis of bronchiolitis who required fluid therapy. The trials compared enteral tube fluid therapy with parenteral fluid therapy. The primary outcome was difference in length of hospital stay in hours after each non-oral fluid therapy modality. As actual time of discharge can be impacted by various factors, we also assessed theoretical length of stay (i.e. time when a patient is safe for discharge). We assessed several secondary outcomes.

Data collection and analysis: We used standard methodological procedures expected by Cochrane. MAIN RESULTS: The searches yielded 615 unique records, of which four articles underwent full-text screening. We included two trials (810 children). Oakley 2013 was an open, non-blinded RCT of infants aged two to 12 months admitted to hospitals in Australia and New Zealand with a clinical diagnosis of bronchiolitis during three bronchiolitis seasons. The trial enrolled 759 children, of which 381 were randomised to NG tube therapy and 378 to IV therapy. Risk of bias was low in most domains. Kugelman 2013 was an open, non-blinded RCT that enrolled infants aged less than six months with a clinical diagnosis of "moderate bronchiolitis" at a single hospital in Israel. The study enrolled 51 infants, of which 31 were assigned to NG or OG tube therapy and 20 to IV therapy. Risk of bias was unclear in most domains. The application of enteral tube fluid therapy compared to IV fluid therapy probably makes little to no difference for actual length of hospital stay (mean difference (MD) 6.8 hours, 95% confidence interval (CI) -4.7 to 18.4 hours; 2 studies, 810 children, moderate certainty evidence). There was also little to no difference for theoretical length of stay (MD 4.4 hours, 95% CI -3.6 to 12.4 hours; 2 studies, 810 children, moderate certainty evidence). For the secondary outcomes, enteral tube fluid therapy probably makes little to no

difference for time to resume full oral feeding compared to IV fluid therapy (MD 2.8 hours, 95% CI -3.6 to 9.2 hours; 2 studies, 810 children, moderate certainty evidence). The use of enteral tube for fluid therapy probably results in a large increase in the success of insertion of fluid modality at first attempt (risk ratio (RR) 1.52, 95% CI 1.36 to 1.69; 1 study, 617 children, moderate certainty evidence), and probably largely reduces the chances of change in fluid therapy modality (RR 0.52, 95% CI 0.38 to 0.71; 1 study, 759 children, moderate certainty evidence) compared to IV fluid. Oakley 2013 reported 47 local complication events after discharge in the IV fluid group compared to 30 events in the NG tube group. They also evaluated parental satisfaction, which was high with both modalities. Enteral tube fluid therapy makes little to no difference to the duration of oxygen supplementation (MD 2.2 hours, 95% CI -5.0 to 9.5 hours; 2 studies, 810 children, moderate certainty evidence). Compared with the IV fluid therapy group, there was a 17% relative reduction in the number of intensive care unit admissions (RR 0.83, 95% CI 0.47 to 1.46; 1 study, 759 children, moderate certainty evidence) and a 19% relative reduction in number of readmissions to hospital (RR 0.81, 95% CI 0.33 to 2.04; 1 study, 678 children, moderate certainty evidence) in the enteral tube fluid therapy group. Adverse events were uncommon in both trials, with likely little to no differences between groups.

BMJ Glob Health. 2021 Aug;6(8):e006578.
doi: 10.1136/bmjgh-2021-006578.

Community-based amoxicillin treatment for fast breathing pneumonia in young infants 7-59 days old: a cluster randomised trial in rural Bangladesh, Ethiopia, India and Malawi

Enhanced Management of Pneumonia in Community (EMPIC) Study; Yasir B Nisar[1]

Abstract

Introduction: Young infants 7-59 days old with fast breathing pneumonia presented to a primary level health facility receive a 7-day course of amoxicillin as per the WHO guideline. However, community-level health workers (CLHW) are not allowed to treat these infants. This trial evaluated the community level treatment of non-hypoxaemic young infants with fast breathing pneumonia by CLHWs.

Methods: This cluster-randomised, open-label, non-inferiority trial was conducted in rural areas of Bangladesh, Ethiopia, India and Malawi. We randomly allocated clusters (first-level health facility) 1:1, stratified by the population size, to an intervention group (enhanced community case management) or control group (standard community case management). Infants aged 7-59 days with a respiratory rate of ≥60 breaths/min and oxygen saturation (SpO_2) ≥90% were enrolled. In the intervention clusters, these infants were treated with a 7-day course of oral amoxicillin (according to WHO weight bands) and were regularly followed up by CLHWs. In the control clusters, CLHWs continued the standard management (assess and refer after pre-referral antibiotic dose) and followed up according to the national programme guideline. The primary outcome of treatment failure was assessed in both groups by independent outcome assessors on days 6 and 14 after enrolment. Secondary outcomes (accuracy and impact of pulse oximetry) were also assessed.

Results: Between September 2016 and December 2018, we enrolled 2334 infants (1168 in intervention and 1166 in control clusters) from 208 clusters (104 intervention and 104 control). Of 2334, 22 infants with fast breathing were excluded from analysis, leaving 2312 (1155 in intervention clusters and 1157 in control clusters) for intention-to-treat analysis. The

proportion of treatment failure was 5.4% (63/1155) in intervention and 6.3% (73/1157) in the control clusters, including two deaths (0.2%) in each group. The adjusted risk difference for treatment failure between the two groups was -1.0% (95% CI -3.0% to 1.1%). The secondary outcome showed that CLHWs in the intervention clusters performed all recommended steps of pulse oximetry assessment in 94% (1050/1115) of enrolled patients.
Conclusions: The 7-day amoxicillin treatment for 7-59 days old non-hypoxaemic infants with fast breathing pneumonia by CLHWs was non-inferior to the currently recommended referral strategy.

Life (Basel). 2021 Nov 26;11(12):1299.
doi: 10.3390/life11121299.
Intravenous Amoxicillin Plus Intravenous Gentamicin for Children with Severe Pneumonia in Bangladesh: An Open-Label, Randomized, Non-Inferiority Controlled Trial
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Abstract
The World Health Organization (WHO) recommends intravenous (IV) ampicillin and gentamicin as first-line therapy to treat severe pneumonia in children under five years of age. Ampicillin needs to be administered at a six-hourly interval, which requires frequent nursing intervention and bed occupancy for 5-7 days, limiting its utility in resource-poor settings. We compared the efficacy of IV amoxicillin over IV ampicillin, which is a potential alternative drug in treating severe pneumonia in children between 2-59 months. We conducted an unblinded, randomized, controlled, non-inferiority trial in the Dhaka hospital of icddr,b from 1 January 2018 to 31 October 2019. Children from 2-59 months of age presenting with WHO defined severe pneumonia with respiratory danger signs were randomly assigned 1:1 to either 50 mg/kg ampicillin or 40 mg/kg amoxicillin per day with 7.5 mg/kg gentamicin. The primary outcome was treatment failure as per the standard definition of persistence of danger sign(s) of severe pneumonia beyond 48 h or deterioration within 24 h of therapy initiation. The secondary outcomes were: (i) time required for resolution of danger signs since enrolment, (ii) length of hospital stay, (iii) death during hospitalization, and (iv) rate of nosocomial infections. Among 308 enrolled participants, baseline characteristics were similar among the two groups. Sixty-two (20%) children ended up with treatment failure, 21 (14%) in amoxicillin, and 41 (27%) in ampicillin arm, which is statistically significant (relative risk [RR] 0.51, 95% CI 0.32-0.82; $p = 0.004$). We reported 14 deaths for serious adverse events, 4 (3%) and 10 (6%) among amoxicillin and ampicillin arm, respectively. IV amoxicillin and IV gentamicin combination is not inferior to combined IV ampicillin and IV gentamicin in treating severe pneumonia in under-five children in Bangladesh. Considering the less frequent dosing and more compliance, IV amoxicillin is a better choice for treating children with severe pneumonia in resource-limited settings.

Prevention of pneumonia

(see indoor air pollution)

Oxygen therapy and CPAP for ALRI

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Oxygen systems and quality of care for children with pneumonia, malaria and diarrhoea: Analysis of a stepped-wedge trial in Nigeria

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Abstract

Objectives: To evaluate the effect of improved hospital oxygen systems on quality of care (QOC) for children with severe pneumonia, severe malaria, and diarrhoea with severe dehydration.

Design: Stepped-wedge cluster randomised trial (unblinded), randomised at hospital-level.

Setting: 12 hospitals in south-west Nigeria.

Participants: 7,141 children (aged 28 days to 14 years) admitted with severe pneumonia, severe malaria or diarrhoea with severe dehydration between January 2014 and October 2017.

Interventions: Phase 1 (pulse oximetry) introduced pulse oximetry for all admitted children. Phase 2 (full oxygen system) (i) standardised oxygen equipment package, (ii) clinical education and support, (iii) technical training and support, and (iv) infrastructure and systems support.

Outcome measures: We used quantitative QOC scores evaluating assessment, diagnosis, treatment, and monitoring practices against World Health Organization and Nigerian standards. We evaluated mean differences in QOC scores between study periods (baseline, oximetry, full oxygen system), using mixed-effects linear regression.

Results: 7,141 eligible participants; 6,893 (96.5%) had adequate data for analysis. Mean paediatric QOC score (maximum 6) increased from 1.64 to 3.00 (adjusted mean difference 1.39; 95% CI 1.08-1.69, p<0.001) for severe pneumonia and 2.81 to 4.04 (aMD 1.53; 95% CI 1.23-1.83, p<0.001) for severe malaria, comparing the full intervention to baseline, but did not change for diarrhoea with severe dehydration (aMD -0.12; 95% CI -0.46-0.23, p = 0.501). After excluding practices directly related to pulse oximetry and oxygen, we found aMD 0.23 for severe pneumonia (95% CI -0.02-0.48, p = 0.072) and 0.65 for severe malaria (95% CI 0.41-0.89, p<0.001) comparing full intervention to baseline. Sub-analysis showed some improvements (and no deterioration) in care processes not directly related to oxygen or pulse oximetry.

Conclusion: Improvements in hospital oxygen systems were associated with higher QOC scores, attributable to better use of pulse oximetry and oxygen as well as broader improvements in clinical care, with no negative distortions in care practices.

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Continuous positive airway pressure (CPAP) for acute bronchiolitis in children

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Abstract

Background: Acute bronchiolitis is one of the most frequent causes of emergency department visits and hospitalisation in children up to three years of age. There is no specific treatment for bronchiolitis except for supportive treatment, which includes ensuring adequate hydration and oxygen supplementation. Continuous positive airway pressure (CPAP) aims to widen the lungs' peripheral airways, enabling deflation of overdistended lungs in bronchiolitis. Increased airway pressure also prevents the collapse of poorly supported peripheral small airways during expiration. Observational studies report that CPAP is beneficial for children with acute bronchiolitis. This is an update of a review first published in 2015 and updated in 2019.

Objectives: To assess the efficacy and safety of CPAP compared to no CPAP or sham CPAP in infants and children up to three years of age with acute bronchiolitis.

Search methods: We conducted searches of CENTRAL (2021, Issue 7), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (1946 to August 2021), Embase (1974 to August 2021), CINAHL (1981 to August 2021), and LILACS (1982 to August 2021) in August 2021. We also searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for completed and ongoing trials on 26 October 2021.

Selection criteria: We considered randomised controlled trials (RCTs), quasi-RCTs, cross-over RCTs, and cluster-RCTs evaluating the effect of CPAP in children with acute bronchiolitis.

Data collection and analysis: Two review authors independently assessed study eligibility, extracted data using a structured pro forma, analysed data, and performed meta-analyses. We used the Cochrane risk of bias tool to assess risk of bias in the included studies. We created a summary of the findings table employing GRADEpro GDT software. MAIN RESULTS: We included three studies with a total of 122 children (62/60 in intervention/control arms) aged up to 12 months investigating nasal CPAP compared with supportive (or 'standard') therapy. We included one new trial (72 children) in the 2019 update that contributed data to the assessment of respiratory rate and the need for mechanical ventilation for this update. We did not identify any new trials for inclusion in the current update. The included studies were single-centre trials conducted in France, the UK, and India. Two studies were parallel-group RCTs, and one study was a cross-over RCT. The evidence provided by the included studies was of low certainty; we made an assessment of high risk of bias for blinding, incomplete outcome data, and selective reporting, and confidence intervals were wide. The effect of CPAP on the need for mechanical ventilation in children with acute bronchiolitis was uncertain due to risk of bias and imprecision around the effect estimate (risk difference -0.01, 95% confidence interval (CI) -0.09 to 0.08; 3 RCTs, 122 children; low certainty evidence). None of the trials measured time to recovery. Limited, low certainty evidence indicated that CPAP decreased respiratory rate (decreased respiratory rate is better) (mean difference (MD) -3.81, 95% CI -5.78 to -1.84; 2 RCTs, 91 children; low certainty evidence). Only one trial measured change in arterial oxygen saturation (increased oxygen saturation is better), and the results were imprecise (MD -1.70%, 95% CI -3.76 to 0.36; 1 RCT, 19 children; low certainty evidence). The effect of CPAP on change in arterial partial carbon dioxide pressure (pCO_2) (decrease in pCO_2 is better) was imprecise (MD -2.62 mmHg, 95% CI -5.29 to 0.05; 2 RCTs, 50 children; low

certainty evidence). Duration of hospital stay was similar in both the CPAP and supportive care groups (MD 0.07 days, 95% CI -0.36 to 0.50; 2 RCTs, 50 children; low certainty evidence). Two studies did not report pneumothorax, but pneumothorax did not occur in one study. No studies reported occurrences of deaths. Several outcomes (change in partial oxygen pressure, hospital admission rate (from the emergency department to hospital), duration of emergency department stay, and need for intensive care unit admission) were not reported in the included studies.
Authors' conclusions: The use of CPAP did not reduce the need for mechanical ventilation in children with bronchiolitis, although the evidence was of low certainty. Limited, low certainty evidence suggests that breathing improved (a decreased respiratory rate) in children with bronchiolitis who received CPAP; this finding is unchanged from the 2015 review and 2019 update. Due to the limited available evidence, the effect of CPAP in children with acute bronchiolitis is uncertain for our other outcomes. Larger, adequately powered trials are needed to evaluate the effect of CPAP for children with acute bronchiolitis.

Asthma

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Does the routine use of spirometry improve clinical outcomes in children?-A systematic review
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Abstract
Spirometry provides a quantitative measure of lung function and its use is recommended as an adjunct to enhance pediatric respiratory healthcare in many clinical practice guidelines. However, there is limited evidence confirming the benefits (or otherwise) of using spirometry from either clinician or patient perspectives. This systematic review aimed to determine the impact of spirometry on change in clinical decision making and patient-reported outcome measures. We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, www.clinicaltrials.gov, and World Health Organization International Clinical Trials Registry Platform, from inception to July 2021. We included randomized controlled trials (RCTs) comparing the use versus non-use of spirometry during standard clinical review in children aged <18 years with respiratory problems in clinics. We used Cochrane methodology. The search identified 3475 articles; 8 full-text articles were reviewed but only 1 study fulfilled the inclusion criteria. The single study involved two cluster RCTs of spirometry for children with asthma in general practice. The included study did not find any significant intergroup difference at the 12-month follow-up for asthma-related quality-of-life and clinical endpoints. However, the findings were limited by methodological weaknesses and high risks of bias. With a paucity of data, the clinical benefits of spirometry remain unclear. Thus, there is a clear need for RCTs that provide high-quality evidence to support the routine use of spirometry in children with suspected or known lung disease. Pending the availability of

better evidence, we recommend that clinicians adhere to the current clinical practice recommendations.

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Digital interventions to improve adherence to maintenance medication in asthma

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Abstract

Background: Asthma is the most common chronic lung condition worldwide, affecting 334 million adults and children globally. Despite the availability of effective treatment, such as inhaled corticosteroids (ICS), adherence to maintenance medication remains suboptimal. Poor ICS adherence leads to increased asthma symptoms, exacerbations, hospitalisations, and healthcare utilisation. Importantly, suboptimal use of asthma medication is a key contributor to asthma deaths. The impact of digital interventions on adherence and asthma outcomes is unknown.

Objectives: To determine the effectiveness of digital interventions for improving adherence to maintenance treatments in asthma.

Search methods: We identified trials from the Cochrane Airways Trials Register, which contains studies identified through multiple electronic searches and handsearches of other sources. We also searched trial registries and reference lists of primary studies. We conducted the most recent searches on 1 June 2020, with no restrictions on language of publication. A further search was run in October 2021, but studies were not fully incorporated.

Selection criteria: We included randomised controlled trials (RCTs) including cluster- and quasi-randomised trials of any duration in any setting, comparing a digital adherence intervention with a non-digital adherence intervention or usual care. We included adults and children with a clinical diagnosis of asthma, receiving maintenance treatment.

Data collection and analysis: We used standard methodological procedures for data collection. We used GRADE to assess quantitative outcomes where data were available.

Main results: We included 40 parallel randomised controlled trials (RCTs) involving adults and children with asthma (n = 15,207), of which eight are ongoing studies. Of the included studies, 30 contributed data to at least one meta-analysis. The total number of participants ranged from 18 to 8517 (median 339). Intervention length ranged from two to 104 weeks. Most studies (n = 29) reported adherence to maintenance medication as their primary outcome; other outcomes such as asthma control and quality of life were also commonly reported. Studies had low or unclear risk of selection bias but high risk of performance and detection biases due to inability to blind the participants, personnel, or outcome assessors. A quarter of the studies had high risk of attrition bias and selective outcome reporting. We examined the effect of digital interventions using meta-analysis for the following outcomes: adherence (16 studies); asthma control (16 studies); asthma exacerbations (six studies); unscheduled healthcare utilisation (four studies); lung function (seven studies); and quality of life (10 studies). Pooled results showed that patients receiving digital interventions may have increased adherence (mean difference of 14.66 percentage points, 95% confidence interval (CI) 7.74 to 21.57; low-certainty evidence); this is likely to be clinically significant in

those with poor baseline medication adherence. Subgroup analysis by type of intervention was significant (P = 0.001), with better adherence shown with electronic monitoring devices (EMDs) (23 percentage points over control, 95% CI 10.84 to 34.16; seven studies), and with short message services (SMS) (12 percentage points over control, 95% CI 6.22 to 18.03; four studies). No significant subgroup differences were seen for interventions having an in-person component versus fully digital interventions, adherence feedback, one or multiple digital components to the intervention, or participant age. Digital interventions were likely to improve asthma control (standardised mean difference (SMD) 0.31 higher, 95% CI 0.17 to 0.44; moderate-certainty evidence) - a small but likely clinically significant effect. They may reduce asthma exacerbations (risk ratio 0.53, 95% CI 0.32 to 0.91; low-certainty evidence). Digital interventions may result in a slight change in unscheduled healthcare utilisation, although some studies reported no or a worsened effect. School or work absence data could not be included for meta-analysis due to the heterogeneity in reporting and the low number of studies. They may result in little or no difference in lung function (forced expiratory volume in one second (FEV_1)): there was an improvement of 3.58% predicted FEV_1, 95% CI 1.00% to 6.17%; moderate-certainty evidence); however, this is unlikely to be clinically significant as the FEV_1 change is below 12%. Digital interventions likely increase quality of life (SMD 0.26 higher, 95% CI 0.07 to 0.45; moderate-certainty evidence); however, this is a small effect that may not be clinically significant. Acceptability data showed positive attitudes towards digital interventions. There were no data on cost-effectiveness or adverse events. Our confidence in the evidence was reduced by risk of bias and inconsistency.
Authors' conclusions: Overall, digital interventions may result in a large increase in adherence (low-certainty evidence). There is moderate-certainty evidence that digital adherence interventions likely improve asthma control to a degree that is clinically significant, and likely increase quality of life, but there is little or no improvement in lung function. The review found low-certainty evidence that digital interventions may reduce asthma exacerbations. Subgroup analyses show that EMDs may improve adherence by 23% and SMS interventions by 12%, and interventions with an in-person element and adherence feedback may have greater benefits for asthma control and adherence, respectively. Future studies should include percentage adherence as a routine outcome measure to enable comparison between studies and meta-analysis, and use validated questionnaires to assess adherence and outcomes.

Adolescent health

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Feasibility and acceptability of a multicomponent, group psychological intervention for adolescents with psychosocial distress in public schools of Pakistan: a feasibility cluster randomized controlled trial (cRCT)
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Abstract

Background: Child and adolescent mental health problems are a global public mental health priority. However, there is a lack of evidence-based scalable psychological interventions for adolescents living in low resource settings. This trial was designed to evaluate the feasibility and acceptability of delivering the World Health Organization's Early Adolescent Skills for Emotions (EASE) intervention at public schools in a rural sub-district in Rawalpindi, Pakistan.
Methods: A two arm, single blinded, feasibility cluster randomized controlled trial with mixed-methods evaluation was conducted with 59 adolescents and their caregivers from 8 public schools. In the 4 intervention arm schools, 6 non-specialist facilitators delivered the culturally-adapted EASE group sessions to the adolescents (n = 29) and their caregivers with desired fidelity under the supervision of in-country supervisors.
Results: The participation rate of adolescents in the intervention sessions was 83%. The intervention strategies were implemented by the adolescents. However, attending biweekly sessions at schools was challenging for caregivers with only 50% caregivers attending the sessions.
Conclusions: The results of this study support the feasibility and acceptability of delivering this culturally adapted intervention through non-specialist facilitators in school settings in Pakistan and pave the way to conduct a fully powered cluster randomized controlled trial to test the effectiveness of intervention to improve psychological outcomes in adolescents.
Trial registration Trial registered with Clinicaltrials.gov prospectively; NCT04254393.

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Feasibility trial of a brief scalable psychological intervention for Syrian refugee adolescents in Jordan

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Abstract
Background: Most refugees are less than 18 years and at heightened risk of common mental disorders (CMDs) relative to other youth. Limited evidence exists for psychosocial programsfor youth in low-resource settings. Early Adolescent Skills for Emotions (EASE) was developed by the World Health Organization to address this gap.
Objectives: This study tested the safety, feasibility, and trial procedures of the EASE intervention among Syrian refugee youth in preparation for a definitive randomized controlled trial (RCT).
Methods: A feasibility RCT was conducted in Amman, Jordan with Syrian children aged 10-14 years who reported psychological distress. Following community screening, youth and their caregivers were randomized to receive either the EASE intervention or enhanced treatment as usual (ETAU). EASE comprised seven group sessions teaching children coping skills, and caregivers received three group sessions to augment the youth sessions. Assessments were conducted at baseline and 1 week following the last EASE session (8 weeks following baseline). Following the trial, a qualitative process evaluation with staff and beneficiaries took place. Primary outcomes were safety and feasibility indicators, and distress was measured by the Paediatric Symptom Checklist.

Results: In November 2018, 179 children were screened; 61 (33%) met criteria for distress (34.1%), two were excluded for suicidal risk, and 59 were randomized (EASE = 33, ETAU = 26). Of those who received EASE, 26 children (79%) completed the intervention. Group attendance was high and no adverse events were reported in either arm. Psychological distress did not show signs of abating in either group over time.
Conclusion: This feasibility trial demonstrated the safety and acceptability of the intervention. Important lessons were learnt regarding entry criteria into the study and engagement of caregivers in the intervention. A fully powered randomized controlled trial will be conducted to evaluate the efficacy of EASE.

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The ARMADILLO text message intervention to improve the sexual and reproductive health knowledge of adolescents in Peru: Results of a randomized controlled trial

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Abstract
Background: The ARMADILLO Study determined whether adolescents able to access SRH information on-demand via SMS were better able to reject contraception-related myths and misconceptions as compared with adolescents receiving pushed SMS or no intervention.
Trial design: This trial was an unblinded, three-arm, parallel-group, individual RCT with a 1:1:1 allocation. Trial registration: ISRCTN85156148.
Methods: This study was conducted in Lima, Peru among participants ages 13-17 years. Eligible participants were randomized into one of three arms: Arm 1: access to ARMADILLO's SMS information on-demand; Arm 2 access to ARMADILLO SMS information pushed to their phone; Arm 3 control (no SMS). The intervention period lasted seven weeks. At baseline, endline, and follow-up (eight weeks following endline), participants were assessed on a variety of contraception-related myths and misconceptions. An index of myths-believed was generated. The primary outcome assessed the subject-specific change in the mean score between baseline and endline. Knowledge retention from endline to follow-up was also assessed, as was a 'content exposure' outcome, which assessed change in participants' knowledge based on relevant SMS received.
Results: In total, 712 participants were randomized to the three arms: 659 completed an endline assessment and were included in the primary analysis. Arm 2 participants believed fewer myths at endline compared with control arm participants (estimated subject-specific mean difference of -3.69% [-6.17%, -1.21%], p = 0.004). There was no significant difference between participants in Arm 1 vs. the control Arm, or between participants in Arm 1 vs. Arm 2. A further decrease in myths believed between endline and follow-up (knowledge retention) was observed in all arms; however, there was no difference between arms. The content exposure analysis saw significant reductions in myths believed for Arm 1 (estimated subject-specific mean difference of -9.47% [-14.83%, -4.11%], p = .001) and Arm 2 (-5.93% [-8.57%, -3.29%], p < .001) as compared with the control arm; however Arm 1's reduced sample size (n = 28) is a severe limitation.
Discussion: The ARMADILLO SMS content has a significant (but small) effect on participants' contraception-related knowledge. Standalone, adolescent SRH digital health interventions

may affect only modest change. Instead, digital is probably best used a complementary channel to expand the reach of existing validated SRH information and service programs.

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Busting contraception myths and misconceptions among youth in Kwale County, Kenya: results of a digital health randomised control trial

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Abstract

Objectives: The objective of this randomised controlled trial in Kenya was to assess the effect of delivering sexual and reproductive health (SRH) information via text message to young people on their ability to reject contraception-related myths and misconceptions.

Design and setting: A three-arm, unblinded randomised controlled trial with a ratio of 1:1:1 in Kwale County, Kenya.

Participants and interventions: A total of 740 youth aged 18-24 years were randomised. Intervention arm participants could access informational SRH text messages on-demand. Contact arm participants received once weekly texts instructing them to study on an SRH topic on their own. Control arm participants received standard care. The intervention period was 7 weeks.

Primary outcome: We assessed change myths believed at baseline and endline using an index of 10 contraception-related myths. We assessed change across arms using difference of difference analysis.

Results: Across arms, <5% of participants did not have any formal education, <10% were living alone, about 50% were single and >80% had never given birth. Between baseline and endline, there was a statistically significant drop in the average absolute number of myths and misconceptions believed by intervention arm (11.1%, 95% CI 17.1% to 5.2%), contact arm (14.4%, 95% CI 20.5% to 8.4%) and control arm (11.3%, 95% CI 17.4% to 5.2%) participants. However, we observed no statistically significant difference in the magnitude of change across arms.

Conclusions: We are unable to conclusively state that the text message intervention was better than text message 'contact' or no intervention at all. Digital health likely has potential for improving SRH-related outcomes when used as part of multifaceted interventions. Additional studies with physical and geographical separation of different arms is warranted.

Adolescents and HIV prevention and treatment

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Process evaluation of peer-to-peer delivery of HIV self-testing and sexual health information to support HIV prevention among youth in rural KwaZulu-Natal, South Africa: qualitative analysis

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Abstract

Objective: Peer-to-peer (PTP) HIV self-testing (HIVST) distribution models can increase uptake of HIV testing and potentially create demand for HIV treatment and pre-exposure prophylaxis (PrEP). We describe the acceptability and experiences of young women and men participating in a cluster randomised trial of PTP HIVST distribution and antiretroviral/PrEP promotion in rural KwaZulu-Natal.

Methods: Between March and September 2019, 24 pairs of trained peer navigators were randomised to two approaches to distribute HIVST packs (kits+HIV prevention information): *incentivised-peer-networks* where peer-age friends distributed packs within their social network for a small incentive, or *direct distribution* where peer navigators distributed HIVST packs directly. S*tandard-of-care* peer navigators distributed information without HIVST kits. For the process evaluation, we conducted semi-structured interviews with purposively sampled young women (n=30) and men (n=15) aged 18-29 years from all arms. Qualitative data were transcribed, translated, coded manually and thematically analysed using an interpretivist approach.

Results: Overall, PTP approaches were acceptable and valued by young people. Participants were comfortable sharing sexual health issues they would not share with adults. Coupled with HIVST, peer (friends) support facilitated HIV testing and solidarity for HIV status disclosure and treatment. However, some young people showed limited interest in other sexual health information provided. Some young people were wary of receiving health information from friends perceived as non-professionals while others avoided sharing personal issues with peer navigators from their community. Referral slips and youth-friendly clinics were facilitators to PrEP uptake. Family disapproval, limited information, daily pills and perceived risks were major barriers to PrEP uptake.

Conclusion: Both professional (peer navigators) and social network (friends) approaches were acceptable methods to receive HIVST and sexual health information. Doubts about the professionalism of friends and overly exclusive focus on HIVST information materials may in part explain why HIVST kits, without peer navigators support, did not create demand for PrEP.

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From surviving to thriving: integrating mental health care into HIV, community, and family services for adolescents living with HIV

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Abstract
Adolescents are a crucial generation, with the potential to bring future social and economic success for themselves and their countries. More than 90% of adolescents living with HIV reside in sub-Saharan Africa, where their mental health is set against a background of poverty, familial stress, service gaps, and an HIV epidemic that is now intertwined with the COVID-19 pandemic. In this Series paper, we review systematic reviews, randomised trials, and cohort studies of adolescents living with and affected by HIV. We provide a detailed overview of mental health provision and collate evidence for future approaches. We find that the mental health burden for adolescents living with HIV is high, contributing to low quality of life and challenges with adherence to antiretroviral therapy. Mental health provision is scarce, infrastructure and skilled providers are missing, and leadership is needed. Evidence of effective interventions is emerging, including specific provisions for mental health (eg, cognitive behavioural therapy, problem-solving, mindfulness, and parenting programmes) and broader provisions to prevent drivers of poor mental health (eg, social protection and violence prevention). We provide evidence of longitudinal associations between unconditional government grants and improved mental health. Combinations of economic and social interventions (known as cash plus care) could increase mental health benefits. Scalable delivery models include task sharing, primary care integration, strengthening families, and a pyramid of provision that differentiates between levels of need, from prevention to the care of severe disorders. A turning point has now been reached, from which complacency cannot persist. We conclude that there is substantial need, available frameworks, and a growing evidence base for action while infrastructure and skill acquisition is built.

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Psychosocial interventions for improving engagement in care and health and behavioural outcomes for adolescents and young people living with HIV: a systematic review and meta-analysis

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Abstract
Introduction: Adolescents and young people comprise a growing proportion of new HIV infections globally, yet current approaches do not effectively engage this group, and adolescent HIV-related outcomes are the poorest among all age groups. Providing psychosocial interventions incorporating psychological, social, and/or behavioural approaches offer a potential pathway to improve engagement in care and health and behavioural outcomes among adolescents and young people living with HIV (AYPLHIV).
Methods: A systematic search of all peer-reviewed papers published between January 2000 and July 2020 was conducted through four electronic databases (Cochrane Library, PsycINFO, PubMed and Scopus). We included randomized controlled trials evaluating psychosocial interventions aimed at improving engagement in care and health and behavioural outcomes of AYPLHIV aged 10 to 24 years.

Results and discussion: Thirty relevant studies were identified. Studies took place in the United States (n = 18, 60%), sub-Saharan Africa (Nigeria, South Africa, Uganda, Zambia, Zimbabwe) and Southeast Asia (Thailand). Outcomes of interest included adherence to antiretroviral therapy (ART), ART knowledge, viral load data, sexual risk behaviours, sexual risk knowledge, retention in care and linkage to care. Overall, psychosocial interventions for AYPLHIV showed important, small-to-moderate effects on adherence to ART (SMD = 0.3907, 95% CI: 0.1059 to 0.6754, 21 studies, n = 2647) and viral load (SMD = -0.2607, 95% CI -04518 to -0.0696, 12 studies, n = 1566). The psychosocial interventions reviewed did not demonstrate significant impacts on retention in care (n = 8), sexual risk behaviours and knowledge (n = 13), viral suppression (n = 4), undetectable viral load (n = 5) or linkage to care (n = 1) among AYPLHIV. No studies measured transition to adult services. Effective interventions employed various approaches, including digital and lay health worker delivery, which hold promise for scaling interventions in the context of COVID-19.
Conclusions: This review highlights the potential of psychosocial interventions in improving health outcomes in AYPLHIV. However, more research needs to be conducted on interventions that can effectively reduce sexual risk behaviours of AYPLHIV, as well as those that can strengthen engagement in care. Further investment is needed to ensure that these interventions are cost-effective, sustainable and resilient in the face of resource constraints and global challenges such as the COVID-19 pandemic.

Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

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Risk of Infection Associated With Administration of Intravenous Iron: A Systematic Review and Meta-analysis

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Abstract
Importance: Intravenous iron is recommended by many clinical guidelines based largely on its effectiveness in reducing anemia. However, the association with important safety outcomes, such as infection, remains uncertain.
Objective: To examine the risk of infection associated with intravenous iron compared with oral iron or no iron.
Data sources: Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials (RCTs) from 1966 to January 31, 2021. Ongoing trials were sought from ClinicalTrials.gov, CENTRAL, and the World Health Organization International Clinical Trials Search Registry Platform.
Study selection: Pairs of reviewers identified RCTs that compared intravenous iron with oral iron or no iron across all patient populations, excluding healthy volunteers. Nonrandomized

studies published since January 1, 2007, were also included. A total of 312 full-text articles were assessed for eligibility.
Data extraction and synthesis: Data extraction and risk of bias assessments were performed according to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) and Cochrane recommendations, and the quality of evidence was assessed using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach. Two reviewers extracted data independently. A random-effects model was used to synthesize data from RCTs. A narrative synthesis was performed to characterize the reporting of infection.
Main outcomes and measures: The primary outcome was risk of infection. Secondary outcomes included mortality, hospital length of stay, and changes in hemoglobin and red blood cell transfusion requirements. Measures of association were reported as risk ratios (RRs) or mean differences.
Results: A total of 154 RCTs (32 920 participants) were included in the main analysis. Intravenous iron was associated with an increased risk of infection when compared with oral iron or no iron (RR, 1.17; 95% CI, 1.04-1.31; I2 = 37%; moderate certainty of evidence). Intravenous iron also was associated with an increase in hemoglobin (mean difference, 0.57 g/dL; 95% CI, 0.50-0.64 g/dL; I2 = 94%) and a reduction in the risk of requiring a red blood cell transfusion (RR, 0.93; 95% CI, 0.76-0.89; I2 = 15%) when compared with oral iron or no iron. There was no evidence of an effect on mortality or hospital length of stay.
Conclusions and relevance: In this large systematic review and meta-analysis, intravenous iron was associated with an increased risk of infection. Well-designed studies, using standardized definitions of infection, are required to understand the balance between this risk and the potential benefits.

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Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews
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Abstract
Background: Anaemia is a prevalent health problem worldwide. Some types are preventable or controllable with iron supplementation (pills or drops), fortification (sprinkles or powders containing iron added to food) or improvements to dietary diversity and quality (e.g. education or counselling).
Objectives: To summarise the evidence from systematic reviews regarding the benefits or harms of nutrition-specific interventions for preventing and controlling anaemia in anaemic or non-anaemic, apparently healthy populations throughout the life cycle.
Methods: In August 2020, we searched MEDLINE, Embase and 10 other databases for systematic reviews of randomised controlled trials (RCTs) in anaemic or non-anaemic, apparently healthy populations. We followed standard Cochrane methodology, extracting GRADE ratings where provided. The primary outcomes were haemoglobin (Hb) concentration, anaemia, and iron deficiency anaemia (IDA); secondary outcomes were iron deficiency (ID), severe anaemia and adverse effects (e.g. diarrhoea, vomiting).

Main results: We included 75 systematic reviews, 33 of which provided GRADE assessments; these varied between high and very low. Infants (6 to 23 months; 13 reviews) Iron supplementation increased Hb levels and reduced the risk of anaemia and IDA in two reviews. Iron fortification of milk or cereals, multiple-micronutrient powder (MMNP), home fortification of complementary foods, and supplementary feeding increased Hb levels and reduced the risk of anaemia in six reviews. In one review, lipid-based nutrient supplementation (LNS) reduced the risk of anaemia. In another, caterpillar cereal increased Hb levels and IDA prevalence. Food-based strategies (red meat and fortified cow's milk, beef) showed no evidence of a difference (1 review). Preschool and school-aged children (2 to 10 years; 8 reviews) Daily or intermittent iron supplementation increased Hb levels and reduced the risk of anaemia and ID in two reviews. One review found no evidence of difference in Hb levels, but an increased risk of anaemia and ID for the intermittent regime. All suggested that zinc plus iron supplementation versus zinc alone, multiple-micronutrient (MMN)-fortified beverage versus control, and point-of-use fortification of food with iron-containing micronutrient powder (MNP) versus placebo or no intervention may increase Hb levels and reduce the risk of anaemia and ID. Fortified dairy products and cereal food showed no evidence of a difference on the incidence of anaemia (1 review). Adolescent children (11 to 18 years; 4 reviews) Compared with no supplementation or placebo, five types of iron supplementation may increase Hb levels and reduce the risk of anaemia (3 reviews). One review on prevention found no evidence of a difference in anaemia incidence on iron supplementation with or without folic acid, but Hb levels increased. Another suggested that nutritional supplementation and counselling reduced IDA. One review comparing MMN fortification with no fortification observed no evidence of a difference in Hb levels. Non-pregnant women of reproductive age (19 to 49 years; 5 reviews) Two reviews suggested that iron therapy (oral, intravenous (IV), intramuscular (IM)) increased Hb levels; one showed that iron folic acid supplementation reduced anaemia incidence; and another that daily iron supplementation with or without folic acid or vitamin C increased Hb levels and reduced the risk of anaemia and ID. No review reported interventions related to fortification or dietary diversity and quality. Pregnant women of reproductive age (15 to 49 years; 23 reviews) One review apiece suggested that: daily iron supplementation with or without folic acid increased Hb levels in the third trimester or at delivery and in the postpartum period, and reduced the risk of anaemia, IDA and ID in the third trimester or at delivery; intermittent iron supplementation had no effect on Hb levels and IDA, but increased the risk of anaemia at or near term and ID, and reduced the risk of side effects; vitamin A supplementation alone versus placebo, no intervention or other micronutrient might increase maternal Hb levels and reduce the risk of maternal anaemia; MMN with iron and folic acid versus placebo reduced the risk of anaemia; supplementation with oral bovine lactoferrin versus oral ferrous iron preparations increased Hb levels and reduced gastrointestinal side effects; MNP for point-of-use fortification of food versus iron and folic acid supplementation might decrease Hb levels at 32 weeks' gestation and increase the risk of anaemia; and LNS versus iron or folic acid and MMN increased the risk of anaemia. Mixed population (all ages; 22 reviews) Iron supplementation versus placebo or control increased Hb levels in healthy children, adults, and elderly people (4 reviews). Hb levels appeared to increase and risk of anaemia and ID decrease in two reviews investigating MMN fortification versus placebo or no treatment, iron fortified flour versus control, double fortified salt versus iodine only fortified salt, and rice fortification with iron alone or in combination with other micronutrients versus unfortified rice or no intervention. Each review suggested that fortified versus non-fortified condiments

or noodles, fortified (sodium iron ethylenediaminetetraacetate; NaFeEDTA) versus non-fortified soy sauce, and double-fortified salt versus control salt may increase Hb concentration and reduce the risk of anaemia. One review indicated that Hb levels increased for children who were anaemic or had IDA and received iron supplementation, and decreased for those who received dietary interventions. Another assessed the effects of foods prepared in iron pots, and found higher Hb levels in children with low-risk malaria status in two trials, but no difference when comparing food prepared in non-cast iron pots in a high-risk malaria endemicity mixed population. There was no evidence of a difference for adverse effects. Anaemia and malaria prevalence were rarely reported. No review focused on women aged 50 to 65 years plus or men (19 to 65 years plus).
Authors' conclusions: Compared to no treatment, daily iron supplementation may increase Hb levels and reduce the risk of anaemia and IDA in infants, preschool and school-aged children and pregnant and non-pregnant women. Iron fortification of foods in infants and use of iron pots with children may have prophylactic benefits for malaria endemicity low-risk populations. In any age group, only a limited number of reviews assessed interventions to improve dietary diversity and quality. Future trials should assess the effects of these types of interventions, and consider the requirements of different populations.

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Benefits and Risks of Iron Interventions in Infants in Rural Bangladesh

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Abstract
Background: Universal provision of iron supplements (drops or syrup) or multiple micronutrient powders to young children in low-to-middle-income countries where anemia is prevalent is recommended by the World Health Organization and widely implemented. The functional benefits and safety of these interventions are unclear.
Methods: We conducted a three-group, double-blind, double-dummy, individually randomized, placebo-controlled trial to assess the immediate and medium-term benefits and risks of 3 months of daily supplementation with iron syrup or iron-containing multiple micronutrient powders, as compared with placebo, in 8-month-old children in rural Bangladesh. The primary outcome was cognitive development, as assessed by the cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition, immediately after completion of the assigned 3-month regimen; scores range from 55 to 145, with higher scores indicating better cognitive performance. Secondary outcomes included the cognitive composite score at 9 months after completion of the assigned regimen; behavioral, language, and motor development, as well as growth and hematologic markers, immediately after completion and at 9 months after completion; and safety.
Results: We randomly assigned 3300 infants to receive iron syrup (1101 infants), multiple micronutrient powders (1099), or placebo (1100) daily. After completion of the assigned 3-month regimen, no apparent effect on the cognitive composite score was observed with iron syrup as compared with placebo (mean between-group difference in change in score from

baseline, -0.30 points; 95% confidence interval [CI], -1.08 to 0.48) or with multiple micronutrient powders as compared with placebo (mean between-group difference in change in score from baseline, 0.23 points; 95% CI, -0.55 to 1.00). No apparent effect on any other developmental or growth outcome was observed immediately after completion of the assigned regimen or at 9 months after completion. At 9 months after completion of the assigned regimen, the prevalences of anemia, iron deficiency, and iron deficiency anemia increased in all three trial groups but remained lower among the children who received iron syrup or multiple micronutrient powders than among those who received placebo. The risk of serious adverse events and incidence of symptoms of infection were similar in the three trial groups.
Conclusions: In this trial involving infants in Bangladesh, 3 months of daily supplementation with iron syrup or multiple micronutrient powders did not appear to have an effect on child development or other functional outcomes as compared with placebo.

Anaesthesia and intensive care

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Chloral hydrate as a sedating agent for neurodiagnostic procedures in children
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Abstract
Background: This is an updated version of a Cochrane Review published in 2017. Paediatric neurodiagnostic investigations, including brain neuroimaging and electroencephalography (EEG), play an important role in the assessment of neurodevelopmental disorders. The use of an appropriate sedative agent is important to ensure the successful completion of the neurodiagnostic procedures, particularly in children, who are usually unable to remain still throughout the procedure.
Objectives: To assess the effectiveness and adverse effects of chloral hydrate as a sedative agent for non-invasive neurodiagnostic procedures in children.
Search methods: We searched the following databases on 14 May 2020, with no language restrictions: the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid, 1946 to 12 May 2020). CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, the Cochrane Central Register of Controlled Trials (CENTRAL), and the specialised registers of Cochrane Review Groups including Cochrane Epilepsy.
Selection criteria: Randomised controlled trials that assessed chloral hydrate agent against other sedative agent(s), non-drug agent(s), or placebo.
Data collection and analysis: Two review authors independently evaluated studies identified by the search for their eligibility, extracted data, and assessed risk of bias. Results were expressed in terms of risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data, with 95% confidence intervals (CIs).
Main results: We included 16 studies with a total of 2922 children. The methodological quality of the included studies was mixed. Blinding of the participants and personnel was not achieved in most of the included studies, and three of the 16 studies were at high risk of bias

for selective reporting. Evaluation of the efficacy of the sedative agents was also underpowered, with all the comparisons performed in small studies. Fewer children who received oral chloral hydrate had sedation failure compared with oral promethazine (RR 0.11, 95% CI 0.01 to 0.82; 1 study; moderate-certainty evidence). More children who received oral chloral hydrate had sedation failure after one dose compared to intravenous pentobarbital (RR 4.33, 95% CI 1.35 to 13.89; 1 study; low-certainty evidence), but there was no clear difference after two doses (RR 3.00, 95% CI 0.33 to 27.46; 1 study; very low-certainty evidence). Children with oral chloral hydrate had more sedation failure compared with rectal sodium thiopental (RR 1.33, 95% CI 0.60 to 2.96; 1 study; moderate-certainty evidence) and music therapy (RR 17.00, 95% CI 2.37 to 122.14; 1 study; very low-certainty evidence). Sedation failure rates were similar between groups for comparisons with oral dexmedetomidine, oral hydroxyzine hydrochloride, oral midazolam and oral clonidine. Children who received oral chloral hydrate had a shorter time to adequate sedation compared with those who received oral dexmedetomidine (MD -3.86, 95% CI -5.12 to -2.6; 1 study), oral hydroxyzine hydrochloride (MD -7.5, 95% CI -7.85 to -7.15; 1 study), oral promethazine (MD -12.11, 95% CI -18.48 to -5.74; 1 study) (moderate-certainty evidence for three aforementioned outcomes), rectal midazolam (MD -95.70, 95% CI -114.51 to -76.89; 1 study), and oral clonidine (MD -37.48, 95% CI -55.97 to -18.99; 1 study) (low-certainty evidence for two aforementioned outcomes). However, children with oral chloral hydrate took longer to achieve adequate sedation when compared with intravenous pentobarbital (MD 19, 95% CI 16.61 to 21.39; 1 study; low-certainty evidence), intranasal midazolam (MD 12.83, 95% CI 7.22 to 18.44; 1 study; moderate-certainty evidence), and intranasal dexmedetomidine (MD 2.80, 95% CI 0.77 to 4.83; 1 study, moderate-certainty evidence). Children who received oral chloral hydrate appeared significantly less likely to complete neurodiagnostic procedure with child awakening when compared with rectal sodium thiopental (RR 0.95, 95% CI 0.83 to 1.09; 1 study; moderate-certainty evidence). Chloral hydrate was associated with a higher risk of the following adverse events: desaturation versus rectal sodium thiopental (RR 5.00, 95% 0.24 to 102.30; 1 study), unsteadiness versus intranasal dexmedetomidine (MD 10.21, 95% CI 0.58 to 178.52; 1 study), vomiting versus intranasal dexmedetomidine (MD 10.59, 95% CI 0.61 to 185.45; 1 study) (low-certainty evidence for aforementioned three outcomes), and crying during administration of sedation versus intranasal dexmedetomidine (MD 1.39, 95% CI 1.08 to 1.80; 1 study, moderate-certainty evidence). Chloral hydrate was associated with a lower risk of the following: diarrhoea compared with rectal sodium thiopental (RR 0.04, 95% CI 0.00 to 0.72; 1 study), lower mean diastolic blood pressure compared with sodium thiopental (MD 7.40, 95% CI 5.11 to 9.69; 1 study), drowsiness compared with oral clonidine (RR 0.44, 95% CI 0.30 to 0.64; 1 study), vertigo compared with oral clonidine (RR 0.15, 95% CI 0.01 to 2.79; 1 study) (moderate-certainty evidence for aforementioned four outcomes), and bradycardia compared with intranasal dexmedetomidine (MD 0.17, 95% CI 0.05 to 0.59; 1 study; high-certainty evidence). No other adverse events were significantly associated with chloral hydrate, although there was an increased risk of combined adverse events overall (RR 7.66, 95% CI 1.78 to 32.91; 1 study; low-certainty evidence).

Authors' conclusions: The certainty of evidence for the comparisons of oral chloral hydrate against several other methods of sedation was variable. Oral chloral hydrate appears to have a lower sedation failure rate when compared with oral promethazine. Sedation failure was similar between groups for other comparisons such as oral dexmedetomidine, oral hydroxyzine hydrochloride, and oral midazolam. Oral chloral hydrate had a higher sedation

failure rate when compared with intravenous pentobarbital, rectal sodium thiopental, and music therapy. Chloral hydrate appeared to be associated with higher rates of adverse events than intranasal dexmedetomidine. However, the evidence for the outcomes for oral chloral hydrate versus intravenous pentobarbital, rectal sodium thiopental, intranasal dexmedetomidine, and music therapy was mostly of low certainty, therefore the findings should be interpreted with caution. Further research should determine the effects of oral chloral hydrate on major clinical outcomes such as successful completion of procedures, requirements for an additional sedative agent, and degree of sedation measured using validated scales, which were rarely assessed in the studies included in this review. The safety profile of chloral hydrate should be studied further, especially for major adverse effects such as oxygen desaturation.

Antibiotics

Antibiotic resistance and stewardship

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Antimicrobial Prescribing during Infant Hospital Admissions in a Birth Cohort in Dhaka, Bangladesh

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Abstract

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

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Effects of screening strategies to detect carbapenem-resistant gram-negative bacteria: A systematic review

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Abstract

Objective: This systematic review aims to summarize the evidence on the effects of screening strategies to detect carbapenem-resistant gram-negative bacteria (Enterobacteriaceae, Acinetobacter baumannii, and Pseudomonas aeruginosa).

Methods: Eligible studies were randomized trials, non-randomized controlled trials, controlled before-after studies, and interrupted time series. We conducted searches in CENTRAL, PUBMED, Embase, Epistemonikos, and in multiple databases available in the Virtual Health Library (LILACS, Scielo, WHO IBECS, and PAHO IBECS). All the searches covered the period until 4 June 2021. No date or language restrictions were applied. Two reviewers independently evaluated potentially eligible studies according to predefined selection criteria, and extracted data on study characteristics, methods, outcomes, and risk of bias, using a predesigned standardized form. When possible, we intended to conduct meta-analyses using a random-effect model. We assessed the certainty of the evidence (CoE) and summarized the results using the GRADE approach.

Results: Our search strategy yielded 57,451 references. No randomized trials were identified. Sixteen studies (one controlled before-after study and 15 interrupted time series) met our inclusion criteria and were included in the review. Most studies were conducted in tertiary care general hospitals from the United States, Europe, and Asia. Eleven studies included adult patients hospitalized in general wards and intensive care units, one was carried out in a neonatal intensive care unit, two in hematology or oncology units, and one in a solid organ transplantation department. Eleven studies were conducted in the setting of an outbreak. Regarding the detection strategy used, all studies included screening strategies for high-risk patients at the moment of admission and 7 studies reported a contact surveillance strategy. Most studies were conducted in settings where infection prevention and control measures were concomitantly installed or reinforced. Data were not suitable for meta-analysis, so the results were presented as a narrative synthesis. Most studies showed a decline in the prevalence of both infection and colonization rates after the implementation of a policy of active surveillance, but the CoE is low. Screening strategies may result in little to no difference in the risk of all-cause mortality and the length of hospital stay.

Conclusions: Existing evidence may favor the use of surveillance culture to carbapenem-resistant gram-negative bacteria, but its quality is poor, so solid conclusions cannot be drawn. Well-conducted randomized trials or high-quality quasi-experimental studies are needed to improve the certainty of the existing evidence. These studies should assess the effect of the addition of screening strategies as a single intervention and measure clinically important outcomes such as infection, length of hospital stay, and mortality.

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The Impact of Antimicrobial Stewardship in Children in Low- and Middle-income Countries: A Systematic Review

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Abstract

Background: Antimicrobial stewardship (AMS) is central to the World Health Organisation Global Action Plan against antimicrobial resistance (AMR). If antibiotics are used without restraint, morbidity and mortality from AMR will continue to increase. In resource-rich settings, AMS can safely reduce antibiotic consumption. However, for children in low- and middle-income countries (LMIC), the impact of different AMS interventions is unknown.
Aim: To determine the impact of different AMS interventions on antibiotic use and clinical and microbiologic outcomes in children in LMIC.
Methods: MEDLINE, Embase and PubMed were searched for studies of AMS interventions in pediatric population in LMIC settings. Controlled trials, controlled before-and-after studies and interrupted time series studies were included. Outcomes assessed were antibiotic use, multidrug-resistant organism (MDRO) rates, clinical outcomes and cost.
Results: Of 1462 studies, 34 met inclusion criteria including a total population of >5,000,000 in 17 countries. Twenty were in inpatients, 2 in ED, 10 in OPD and 2 in both. Seven studies were randomized controlled trials. All types of interventions reported a positive impact on antibiotic prescribing. AMS bundles with education, and clinical decision tools appeared more effective than guidelines alone. AMS interventions resulted in significantly decreased clinical infections (4/4 studies) and clinical failure (2/2) and reduced MDRO colonization rate (4/4). There was no concomitant increase in mortality (4/4 studies) or length of stay (2/2).
Conclusion: Multiple effective strategies exist to reduce antibiotic consumption in LMIC. However, marked heterogeneity limit conclusions regarding the most effective approach, particularly regarding clinical outcomes. Overall, AMS strategies are important tools in the reduction of MDRO-related morbidity in children in LMIC.

Cash transfers and family economic support

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Unconditional cash transfers for reducing poverty and vulnerabilities: effect on use of health services and health outcomes in low- and middle-income countries

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Abstract

Background: Unconditional cash transfers (UCTs; provided without obligation) for reducing poverty and vulnerabilities (e.g. orphanhood, old age, or HIV infection) are a social protection intervention addressing a key social determinant of health (income) in low- and middle-income countries (LMICs). The relative effectiveness of UCTs compared with conditional cash transfers (CCTs; provided only if recipients follow prescribed behaviours, e.g. use a health service or attend school) is unknown.

Objectives: To assess the effects of UCTs on health services use and health outcomes in children and adults in LMICs. Secondary objectives are to assess the effects of UCTs on social determinants of health and healthcare expenditure, and to compare the effects of UCTs versus CCTs.
Search methods: For this update, we searched 15 electronic academic databases, including CENTRAL, MEDLINE and EconLit, in September 2021. We also searched four electronic grey literature databases, websites of key organisations and reference lists of previous systematic reviews, key journals and included study records.
Selection criteria: We included both parallel-group and cluster-randomised controlled trials (C-RCTs), quasi-RCTs, cohort studies, controlled before-and-after studies (CBAs), and interrupted time series studies of UCT interventions in children (0 to 17 years) and adults (≥ 18 years) in LMICs. Comparison groups received either no UCT, a smaller UCT or a CCT. Our primary outcomes were any health services use or health outcome.
Data collection and analysis: Two review authors independently screened potentially relevant records for inclusion, extracted data and assessed the risk of bias. We obtained missing data from study authors if feasible. For C-RCTs, we generally calculated risk ratios for dichotomous outcomes from crude frequency measures in approximately correct analyses. Meta-analyses applied the inverse variance or Mantel-Haenszel method using a random-effects model. Where meta-analysis was impossible, we synthesised results using vote counting based on effect direction. We assessed the certainty of the evidence using GRADE.
Main results: We included 34 studies (25 studies of 20 C-RCTs, six CBAs, and three cohort studies) involving 1,140,385 participants (45,538 children, 1,094,847 adults) and 50,095 households in Africa, the Americas and South-East Asia in our meta-analyses and narrative syntheses. These analysed 29 independent data sets. The 24 UCTs identified, including one basic universal income intervention, were pilot or established government programmes or research experiments. The cash value was equivalent to 1.3% to 81.9% of the annualised gross domestic product per capita. All studies compared a UCT with no UCT; three studies also compared a UCT with a CCT. Most studies carried an overall high risk of bias (i.e. often selection or performance bias, or both). Most studies were funded by national governments or international organisations, or both. Throughout the review, we use the words 'probably' to indicate moderate-certainty evidence, 'may/maybe' for low-certainty evidence, and 'uncertain' for very low-certainty evidence. Health services use We assumed greater use of any health services to be beneficial. UCTs may not have impacted the likelihood of having used any health service in the previous 1 to 12 months, when participants were followed up between 12 and 24 months into the intervention (risk ratio (RR) 1.04, 95% confidence interval (CI) 1.00 to 1.09; I^2 = 2%; 5 C-RCTs, 4972 participants; low-certainty evidence). Health outcomes At one to two years, UCTs probably led to a clinically meaningful, very large reduction in the likelihood of having had any illness in the previous two weeks to three months (RR 0.79, 95% CI 0.67 to 0.92; I^2 = 53%; 6 C-RCTs, 9367 participants; moderate-certainty evidence). UCTs may have increased the likelihood of having been food secure over the previous month, at 13 to 36 months into the intervention (RR 1.25, 95% CI 1.09 to 1.45; I^2 = 85%; 5 C-RCTs, 2687 participants; low-certainty evidence). UCTs may have increased participants' level of dietary diversity over the previous week, when assessed with the Household Dietary Diversity Score and followed up 24 months into the intervention (mean difference (MD) 0.59 food categories, 95% CI 0.18 to 1.01; I^2 = 79%; 4 C-RCTs, 9347 participants; low-certainty evidence). Despite several studies providing relevant evidence, the effects of UCTs on the likelihood of being moderately stunted and on the level of

depression remain uncertain. We found no study on the effect of UCTs on mortality risk. Social determinants of health UCTs probably led to a clinically meaningful, moderate increase in the likelihood of currently attending school, when assessed at 12 to 24 months into the intervention (RR 1.06, 95% CI 1.04 to 1.09; I^2 = 0%; 8 C-RCTs, 7136 participants; moderate-certainty evidence). UCTs may have reduced the likelihood of households being extremely poor, at 12 to 36 months into the intervention (RR 0.92, 95% CI 0.87 to 0.97; I^2 = 63%; 6 C-RCTs, 3805 participants; low-certainty evidence). The evidence was uncertain for whether UCTs impacted livestock ownership, participation in labour, and parenting quality. Healthcare expenditure Evidence from eight cluster-RCTs on healthcare expenditure was too inconsistent to be combined in a meta-analysis, but it suggested that UCTs may have increased the amount of money spent on health care at 7 to 36 months into the intervention (low-certainty evidence). Equity, harms and comparison with CCTs The effects of UCTs on health equity (or unfair and remedial health inequalities) were very uncertain. We did not identify any harms from UCTs. Three cluster-RCTs compared UCTs versus CCTs with regard to the likelihood of having used any health services or had any illness, or the level of dietary diversity, but evidence was limited to one study per outcome and was very uncertain for all three.

Authors' conclusions: This body of evidence suggests that unconditional cash transfers (UCTs) may not impact a summary measure of health service use in children and adults in LMICs. However, UCTs probably or may improve some health outcomes (i.e. the likelihood of having had any illness, the likelihood of having been food secure, and the level of dietary diversity), two social determinants of health (i.e. the likelihoods of attending school and being extremely poor), and healthcare expenditure. The evidence on the relative effectiveness of UCTs and CCTs remains very uncertain.

Community child health

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Child health and the implementation of Community and District-management Empowerment for Scale-up (CODES) in Uganda: a randomised controlled trial

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Abstract

Introduction: Uganda's district-level administrative units buttress the public healthcare system. In many districts, however, local capacity is incommensurate with that required to plan and implement quality health interventions. This study investigates how a district management strategy informed by local data and community dialogue influences health services.

Methods: A 3-year randomised controlled trial (RCT) comprised of 16 Ugandan districts tested a management approach, Community and District-management Empowerment for Scale-up (CODES). Eight districts were randomly selected for each of the intervention and

comparison areas. The approach relies on a customised set of data-driven diagnostic tools to identify and resolve health system bottlenecks. Using a difference-in-differences approach, the authors performed an intention-to-treat analysis of protective, preventive and curative practices for malaria, pneumonia and diarrhoea among children aged 5 and younger.
Results: Intervention districts reported significant net increases in the treatment of malaria (+23%), pneumonia (+19%) and diarrhoea (+13%) and improved stool disposal (+10%). Coverage rates for immunisation and vitamin A consumption saw similar improvements. By engaging communities and district managers in a common quest to solve local bottlenecks, CODES fostered demand for health services. However, limited fiscal space-constrained district managers' ability to implement solutions identified through CODES.
Conclusion: Data-driven district management interventions can positively impact child health outcomes, with clinically significant improvements in the treatment of malaria, pneumonia and diarrhoea as well as stool disposal. The findings recommend the model's suitability for health systems strengthening in Uganda and other decentralised contexts.

Child protection and family violence

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Adherence to HIV post-exposure prophylaxis for children/adolescents who have been sexually assaulted: A systematic review of barriers, enablers, and interventions
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Abstract
Post-exposure prophylaxis (PEP) is a key intervention for preventing HIV acquisition, including following sexual assault. However, uptake and completion rates for HIV PEP are lowest following sexual assault, with only 40% reporting completing the 28-day course. We undertook a systematic review to assess barriers and enablers to adherence to PEP in children and adolescents following sexual assault and identify potential interventions. Five databases and one conference abstract library were searched using adapted search strategies to identify quantitative and qualitative studies reporting patient-reported barriers and enablers to PEP and randomized trials assessing interventions to improve PEP adherence and completion rates. All searches were conducted up to October 2016; the search was updated in PubMed up to 31 July 2018. 14 studies reported barriers and enablers to PEP adherence. The most commonly cited patient/caregiver reported barriers to PEP adherence/completion included side effects, forgetting, stigma/blame, being busy, poor knowledge, and mental health problems. The most commonly reported factors associated with PEP adherence/completion (reported across 7 studies) included health provider encouragement to take PEP (type of encouragement not described), perpetrator known to be HIV-positive, monetary support for transport, the victim of assault attending counseling, being reminded by family/peers to take PEP, and "one-stop" services offering both HIV testing and PEP at initial consultation. Three randomized trials provided limited evidence supporting the potential benefit of enhanced adherence support for HIV PEP; however, data for children were lacking. Despite low completion rates, there is limited research into causes

of and interventions to improve adherence to PEP following sexual assault, and no direct evidence for children.

Dengue

(see Vaccines - dengue)

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Entomological outcomes of cluster-randomised, community-driven dengue vector-suppression interventions in Kampong Cham province, Cambodia

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Abstract

Cambodia has one of the highest dengue infection rates in Southeast Asia. Here we report quantitative entomological results of a large-scale cluster-randomised trial assessing the impact on vector populations of a package of vector control interventions including larvivorous guppy fish in household water containers, mosquito trapping with gravid-ovitraps, solid waste management, breeding-container coverage through community education and engagement for behavioural change, particularly through the participation of school children. These activities resulted in major reductions in Container Index, House Index, Breteau Index, Pupal Index and Adult Index (all p-values 0.002 or lower) in the Intervention Arm compared with the Control Arm in a series of household surveys conducted over a follow-up period of more than one year, although the project was not able to measure the longer-term sustainability of the interventions. Despite comparative reductions in Adult Index between the study arms, the Adult Index was higher in the Intervention Arm in the final household survey than in the first household survey. This package of biophysical and community engagement interventions was highly effective in reducing entomological indices for dengue compared with the control group, but caution is required in extrapolating the reduction in household Adult Index to a reduction in the overall population of adult Aedes mosquitoes, and in interpreting the relationship between a reduction in entomological indices and a reduction in the number of dengue cases. The package of interventions should be trialled in other locations.

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Field Efficacy of Larvivorous Fish and Pyriproxyfen Combined with Community Engagement on Dengue Vectors in Cambodia: A Randomized Controlled Trial

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Abstract

Evidence on the effectiveness of low-cost, sustainable biological vector control tools for Aedes mosquitoes is limited. Therefore, the purpose of this trial was to estimate the impact of guppy fish in combination with the larvicide pyriproxyfen (PPF) (Sumilarv® 2MR) and communication for behavioral impact (COMBI) activities to reduce entomological indices in Cambodia. In this cluster randomized, controlled superiority trial, 30 clusters comprised of one or more villages each was allocated in a 1:1:1 ratio to receive either 1) all three interventions (guppies, PPF, and COMBI), 2) two interventions (guppies and COMBI), or 3) control (standard vector control). Entomological surveys among 40 randomly selected households per cluster were carried out quarterly. The primary outcome was the population abundance of adult female Aedes mosquitoes trapped using adult resting collections. In the primary analysis, adult female Aedes abundance and mosquito infection rates was aggregated over follow-up time points to give a single rate per cluster. These data were analyzed by negative binomial regression, yielding abundance ratios (ARs). The number of Aedes females was reduced roughly by half compared with the control in both the guppy, PPF, and COMBI arm (AR = 0.54; 95% CI, 0.34-0.85; P = 0.0073); and the guppy and COMBI arm (AR = 0.49; 95% CI, 0.31-0.77; P = 0.0021). The effectiveness demonstrated and extremely low cost of including fish rearing in community-based health structures suggest they should be considered as a vector control tool as long as the benefits outweigh any potential environmental concerns.

See also: BMC Public Health 2017 May 30;17(Suppl 1):433

Early childhood development

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

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Evaluation on the effectiveness on the implementation of WHO caregiver skills training (CST) programme in Hong Kong: a randomised controlled trial protocol

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Abstract

Introduction: This protocol delineates the research design and analytical framework used to evaluate the effectiveness of the WHO-CST (CST, caregiver skills training) in Hong Kong. The WHO-CST aims to enhance the caregiver skills of parents of children with potential autism spectrum disorders (ASD) and/or developmental delays.

Methods and analysis: In this study, 130 eligible caregiver-child dyads were recruited and randomly assigned to the experimental and wait-list-control groups. A randomised controlled trial design was adopted to compare the changes between the two groups regarding caregivers' skills, knowledge and practices when interacting with their children with impairments due to ASD. Assessments were conducted before, immediately after and 1 month after the completion of the WHO-CST programme. The primary measurement tool was the joint engagement rating inventory developed by WHO experts to gauge how parents engage their children. A 10-min video recording of their dyadic interaction and behaviours in a defined play setting was used for the measurement. A set of other measurements of

caregivers' knowledge, confidence and experience of using the caregiving skills were also measured.

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Teaching home-visitors to support responsive caregiving: A cluster randomized controlled trial of an online professional development program in Brazil

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Abstract

Background: Home-visiting programs are a common and effective public health approach to promoting parent and child well-being, including in low- and middle-income countries. The World Health Organization and UNICEF have identified responsive caregiving as one key component of the nurturing care children need to survive and thrive. Nonetheless, the importance of responsive caregiving and how to coach it is often overlooked in trainings for staff in home-visiting programs.

Methods: To determine whether it is possible to enhance home-visitors' understanding of responsive caregiving and how to coach it, we conducted a cluster randomized controlled trial with 181 staff working in Brazil's national home-visiting program. We used a computerized random number generator to randomly assign half of participants to take an online professional development course about responsive caregiving immediately and the other half to a waitlist. Individuals assessing outcome data were blind to group assignment.

Results: Compared to those in the control group (N = 90, both randomized and analyzed), participants assigned to take the course (N = 91, both randomized and analyzed) were more knowledgeable about responsivity (Cohen's *d* = 0.64, 95% Confidence Interval (CI) = 0.34, 0.94) and its importance for children's socioemotional (odds ratio (OR) = 1.88, 95% CI = 1.00, 3.50) and cognitive (OR = 2.57, 95% CI = 1.15, 5.71) development, better able to identify responsive parental behaviors in videotaped interactions (*d* = 1.86, 95% CI = 1.51, 2.21), and suggested more effective strategies for coaching parents on responsivity (*d* = 0.51, 95% CI = 0.21, 0.80) and tracking goal implementation (OR = 3.20, 95% CI = 1.28, 7.99). There were no significant changes in participants' tendency to encourage goal setting and reflection, or their perspective-taking skills. Participants were very satisfied with the course content and mode of delivery and there was no drop-out from the program.

Conclusions: A short, online professional development program created moderate to large improvements in home-visitors' knowledge and intended coaching practices. This suggests that such programs are feasible, even in low-income and rural areas, and provide a low-cost, scalable option for possibly maximizing the impact of home-visiting programs - particularly with regard to parental responsivity, and in turn, child outcomes.

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doi: 10.12688/wellcomeopenres.16591.2. eCollection 2021.

Using the Mothers Object Relations Scale for early childhood development research in rural India: Findings from the Early Life Stress Sub-study of the SPRING Cluster Randomised Controlled Trial (SPRING-ELS)

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Abstract

Background: The World Health Organization and others promote responsive caregiving to support all children to thrive, particularly in low- and middle-income countries. The 14-item Mother's Object Relations Scales - Short Form (MORS-SF) may be of use in research and public health programmes because of its basis in attachment theory and ability to capture parental feelings towards their child. **Methods:** We culturally adapted the MORS-SF for use with mothers in the SPRING home visits trial when their infants were 12 months old. The same dyads were assessed using the HOME inventory concurrently and Bayley Scales of Infant Development III (BSID-III) at 18 months of age. Mixed effects linear regression was used to examine associations between MORS-SF (explanatory variable) and HOME-IT, and the cognitive, language and motor domains of BSID-III (outcome variables). **Results:** 1273 dyads completed all assessments. For the motor and language BSID-III scales and for HOME-IT there were strong and positive associations with the MORS-SF warmth sub-scale, and strong and negative associations with the invasion sub-scale. Important but less strong associations were seen with the BSID-III cognitive scale. Evidence of interaction suggested that both are individually important for child development. **Conclusions:** This is the first time MORS-SF has been used in India where optimising responsive caregiving is of importance in supporting all children to reach their potential. It is also the first time that the tool has been used in relation to child development. MORS-SF could be a valuable addition to evaluation in early childhood development.

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An integrated parenting intervention for maternal depression and child development in a low-resource setting: Cluster randomized controlled trial

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Abstract

Background: Rates of depression among Pakistani mothers are high, leading to poor developmental outcomes in their children. This study tested the effectiveness of a manualized integrated parenting program; Learning through Play Plus (LTP+) for maternal depression in Karachi, Pakistan.

Methods: A cluster randomized control trial conducted from January 2014 to December 2015 across 120 villages in Karachi. A total of 774 depressed mothers aged 18-44 years with children aged 0-30 months old, were included. Villages were randomized to receive LTP+ added to treatment as usual (TAU) or TAU alone. Primary outcomes were severity of maternal depression at 3 and 6 months measured by the Edinburgh Postnatal Depression Scale and child socio-emotional development at 6 months measured by the Ages and Stages Questionnaire (ASQ). Secondary outcomes included maternal anxiety, quality of life, social support, parenting competence, and knowledge about child development.

Results: Mothers in the LTP+ group reported significantly lower depression scores compared to those in the TAU group (6.6 vs. 13.8, effect size [ES]: -7.2; 95% confidence interval [CI]: -8.2, -6.1) at 3 and 6 months (7.2 vs. 12.00; ES: -4.6; 95% CI: -5.9, -3.4). Child socio-emotional

development at 6 months was significantly better in the LTP+ group on all domains of the ASQ. There were also statistically significant improvements on all secondary outcomes at 3- and 6-month follow-up.
Conclusion: In low-resource settings like Pakistan, low-cost integrated parenting interventions delivered by lay health workers can provide effective treatment for depressed mothers, leading to improvements in child development.

Diarrhoea

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

Treatment of diarrhoea

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Effect of 3 Days of Oral Azithromycin on Young Children With Acute Diarrhea in Low-Resource Settings: A Randomized Clinical Trial

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Abstract
Importance: World Health Organization (WHO) guidelines do not recommend routine antibiotic use for children with acute watery diarrhea. However, recent studies suggest that a significant proportion of such episodes have a bacterial cause and are associated with mortality and growth impairment, especially among children at high risk of diarrhea-associated mortality. Expanding antibiotic use among dehydrated or undernourished children may reduce diarrhea-associated mortality and improve growth.
Objective: To determine whether the addition of azithromycin to standard case management of acute nonbloody watery diarrhea for children aged 2 to 23 months who are dehydrated or undernourished could reduce mortality and improve linear growth.

Design, setting, and participants: The Antibiotics for Children with Diarrhea (ABCD) trial was a multicountry, randomized, double-blind, clinical trial among 8266 high-risk children aged 2 to 23 months presenting with acute nonbloody diarrhea. Participants were recruited between July 1, 2017, and July 10, 2019, from 36 outpatient hospital departments or community health centers in a mixture of urban and rural settings in Bangladesh, India, Kenya, Malawi, Mali, Pakistan, and Tanzania. Each participant was followed up for 180 days. Primary analysis included all randomized participants by intention to treat.
Interventions: Enrolled children were randomly assigned to receive either oral azithromycin, 10 mg/kg, or placebo once daily for 3 days in addition to standard WHO case management protocols for the management of acute watery diarrhea.
Main outcomes and measures: Primary outcomes included all-cause mortality up to 180 days after enrollment and linear growth faltering 90 days after enrollment.
Results: A total of 8266 children (4463 boys [54.0%]; mean [SD] age, 11.6 [5.3] months) were randomized. A total of 20 of 4133 children in the azithromycin group (0.5%) and 28 of 4135 children in the placebo group (0.7%) died (relative risk, 0.72; 95% CI, 0.40-1.27). The mean (SD) change in length-for-age z scores 90 days after enrollment was -0.16 (0.59) in the azithromycin group and -0.19 (0.60) in the placebo group (risk difference, 0.03; 95% CI, 0.01-0.06). Overall mortality was much lower than anticipated, and the trial was stopped for futility at the prespecified interim analysis.
Conclusions and relevance: The study did not detect a survival benefit for children from the addition of azithromycin to standard WHO case management of acute watery diarrhea in low-resource settings. There was a small reduction in linear growth faltering in the azithromycin group, although the magnitude of this effect was not likely to be clinically significant. In low-resource settings, expansion of antibiotic use is not warranted. Adherence to current WHO case management protocols for watery diarrhea remains appropriate and should be encouraged.

Diarrhoea prevention

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

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Maternal Underweight and Its Association with Composite Index of Anthropometric Failure among Children under Two Years of Age with Diarrhea in Bangladesh

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Abstract
Malnutrition in women has been a long-standing public health concern, with serious effects on child survival and development. Maternal body mass index (BMI) is an important maternal nutritional indicator. There are few published studies although child anthropometric failures do not occur in isolation and identifying children with single versus several co-occurring failures can better capture cases of growth failure in combination: stunting, wasting, and underweight. In the context of multiple anthropometric failures, traditional markers used to assess children's nutritional status tend to underestimate overall undernutrition. Using the

composite index of anthropometric failure (CIAF), we aimed to assess the association between maternal undernutrition and child undernutrition among children with diarrhea under the age of two and to investigate the correlates. Using 1431 mother-child dyads from the Antibiotic for Children with Diarrhea (ABCD) trial, we extracted children's data at enrollment and on day 90 and day 180 follow-ups. ABCD was a randomized, multi-country, multi-site, double-blind, placebo-controlled clinical trial. The Bangladesh site collected data from July 2017 to July 2019. The outcome variable, CIAF, allows combinations of height-for-age, height-for-weight, and weight-for-age to determine the overall prevalence of undernutrition. The generalized estimating equation was used to explore the correlates of CIAF. After adjusting all the potential covariates, maternal undernutrition status was found to be strongly associated with child undernutrition using the CIAF [aOR: 1.4 (95% CI: 1.0, 1.9), *p*-value = 0.043] among the children with diarrhea under 2 years old. Maternal higher education had a protective effect on CIAF [aOR: 0.7 (95% CI: 0.5, 0.9), *p*-value = 0.033]. Our study findings highlight the importance of an integrated approach focusing on maternal nutrition and maternal education could affect a reduction in child undernutrition based on CIAF.

Epilepsy and acute seizures

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Care delivery and self-management strategies for children with epilepsy

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Abstract

Background: Epilepsy is a neurological disorder affecting both children and adults. Epileptic seizures are the result of excessive and abnormal cortical cell electrical activity in the brain. In response to criticism that epilepsy care for children has little impact on long-term outcomes, healthcare professionals and administrators have developed various service models and strategies to address perceived inadequacies. This is an updated version of a Cochrane Review previously published in 2018.

Objectives: To assess the effects of any specialised or dedicated intervention for epilepsy versus usual care in children and adolescents with epilepsy and their families.

Search methods: We searched the following databases on 14 January 2020: the Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 13 January 2020), PsycINFO (1887 to 14 January 2020), CINAHL Plus (1937 to 14 January 2020), ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. The Cochrane Register of Studies (CRS Web) includes the Cochrane Epilepsy Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL). We also contacted experts in the field seeking information on unpublished and ongoing studies and checked the websites of epilepsy organisations and the reference lists of included studies.

Selection criteria: We included randomised controlled trials recruiting children and adolescents with epilepsy.

Data collection and analysis: Two review authors independently selected trials for inclusion and extracted the relevant data. We assessed the following outcomes: 1. Seizure frequency and severity; 2. Appropriateness and volume of medication prescribed (including evidence of

drug toxicity); 3. Participants' reported knowledge of information and advice received from professionals; 4. Participants' reports of health and quality of life; 5. Objective measures of general health status; 6. Objective measures of social or psychological functioning (including the number of days spent on sick leave/absence from school or work, and employment status); and 7. Costs of care or treatment. The results of the data extraction and quality assessment for each study were presented in structured tables and as a narrative summary. All summary statistics were extracted for each outcome.
Main results: We included nine studies of eight interventions in the review, reporting on seven distinct self-management programmes for educating or counselling children with epilepsy and their parents, and one new model of care. Based largely on self-reported outcomes, each programme showed some benefits for the well-being of children with epilepsy; however, all of the included studies had methodological flaws. No single programme was evaluated with different study samples, and in no instance was the same outcome measured and reported in the same way across studies, precluding any possible meta-analysis, even if the interventions were considered sufficiently similar to include in meta-analysis. We chose the outcomes for which data might be important for decisions about the interventions as per guidance in the Cochrane Handbook for Systematic Reviews of Interventions. We found moderate certainty evidence that one of the educational interventions reduced seizure frequency. There was low certainty evidence that two other educational interventions reduced seizure severity, seizure control, and seizure cure rates. The evidence for all other outcomes (drug adherence, knowledge, self-efficacy and self-perception of epilepsy on quality of life) was mixed.
Authors' conclusions: Whilst each of the programmes evaluated in this review showed some benefit to children with epilepsy, their impact was extremely variable. No programme showed benefits across the full range of outcomes, and all studies had methodological problems. There is currently insufficient evidence in favour of any single programme. Further evidence from randomised controlled trials using validated measures and considering clinical meaningfulness as well as statistical significance of results is required.

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Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data

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Background: This is an updated version of the original Cochrane Review published in 2017. Epilepsy is a common neurological condition with a worldwide prevalence of around 1%. Approximately 60% to 70% of people with epilepsy will achieve a longer-term remission from seizures, and most achieve that remission shortly after starting antiepileptic drug treatment. Most people with epilepsy are treated with a single antiepileptic drug (monotherapy) and current guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom for adults and children recommend carbamazepine or lamotrigine as first-line treatment for focal onset seizures and sodium valproate for generalised onset seizures; however, a range of other antiepileptic drug (AED) treatments are available, and evidence is needed regarding their comparative effectiveness in order to inform treatment choices.

Objectives: To compare the time to treatment failure, remission and first seizure of 12 AEDs (carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, eventrate, zonisamide, eslicarbazepine acetate, lacosamide) currently used as monotherapy in children and adults with focal onset seizures (simple focal, complex focal or secondary generalised) or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus).
Search methods: For the latest update, we searched the following databases on 12 April 2021: the Cochrane Register of Studies (CRS Web), which includes PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Epilepsy Group Specialised Register and MEDLINE (Ovid, 1946 to April 09, 2021). We handsearched relevant journals and contacted pharmaceutical companies, original trial investigators and experts in the field.
Selection criteria: We included randomised controlled trials of a monotherapy design in adults or children with focal onset seizures or generalised onset tonic-clonic seizures (with or without other generalised seizure types).
Data collection and analysis: This was an individual participant data (IPD) and network meta-analysis (NMA) review. Our primary outcome was 'time to treatment failure', and our secondary outcomes were 'time to achieve 12-month remission', 'time to achieve six-month remission', and 'time to first seizure post-randomisation'. We performed frequentist NMA to combine direct evidence with indirect evidence across the treatment network of 12 drugs. We investigated inconsistency between direct 'pairwise' estimates and NMA results via node splitting. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and we assessed the certainty of the evidence using the CiNeMA approach, based on the GRADE framework. We have also provided a narrative summary of the most commonly reported adverse events.
Main results: IPD were provided for at least one outcome of this review for 14,789 out of a total of 22,049 eligible participants (67% of total data) from 39 out of the 89 eligible trials (43% of total trials). We could not include IPD from the remaining 50 trials in analysis for a variety of reasons, such as being unable to contact an author or sponsor to request data, data being lost or no longer available, cost and resources required to prepare data being prohibitive, or local authority or country-specific restrictions. No IPD were available from a single trial of eslicarbazepine acetate, so this AED could not be included in the NMA. Network meta-analysis showed high-certainty evidence that for our primary outcome, 'time to treatment failure', for individuals with focal seizures; lamotrigine performs better than most other treatments in terms of treatment failure for any reason and due to adverse events, including the other first-line treatment carbamazepine; HRs (95% CIs) for treatment failure for any reason for lamotrigine versus: eventrate 1.01 (0.88 to 1.20), zonisamide 1.18 (0.96 to 1.44), lacosamide 1.19 (0.90 to 1.58), carbamazepine 1.26 (1.10 to 1.44), oxcarbazepine 1.30 (1.02 to 1.66), sodium valproate 1.35 (1.09 to 1.69), phenytoin 1.44 (1.11 to 1.85), topiramate 1.50 (1.23 to 1.81), gabapentin 1.53 (1.26 to 1.85), phenobarbitone 1.97 (1.45 to 2.67). No significant difference between lamotrigine and eventrate was shown for any treatment failure outcome, and both AEDs seemed to perform better than all other AEDs. For people with generalised onset seizures, evidence was more limited and of moderate certainty; no other treatment performed better than first-line treatment sodium valproate, but there were no differences between sodium valproate, lamotrigine or eventrate in terms of treatment failure; HRs (95% CIs) for treatment failure for any reason for sodium valproate versus:

lamotrigine 1.06 (0.81 to 1.37), eventrate 1.13 (0.89 to 1.42), gabapentin 1.13 (0.61 to 2.11), phenytoin 1.17 (0.80 to 1.73), oxcarbazepine 1.24 (0.72 to 2.14), topiramate 1.37 (1.06 to 1.77), carbamazepine 1.52 (1.18 to 1.96), phenobarbitone 2.13 (1.20 to 3.79), lacosamide 2.64 (1.14 to 6.09). Network meta-analysis also showed high-certainty evidence that for secondary remission outcomes, few notable differences were shown for either seizure type; for individuals with focal seizures, carbamazepine performed better than gabapentin (12-month remission) and sodium valproate (six-month remission). No differences between lamotrigine and any AED were shown for individuals with focal seizures, or between sodium valproate and other AEDs for individuals with generalised onset seizures. Network meta-analysis also showed high- to moderate-certainty evidence that, for 'time to first seizure,' in general, the earliest licensed treatments (phenytoin and phenobarbitone) performed better than the other treatments for individuals with focal seizures; phenobarbitone performed better than both first-line treatments carbamazepine and lamotrigine. There were no notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, eventrate, zonisamide and lacosamide) for either seizure type. Generally, direct evidence (where available) and network meta-analysis estimates were numerically similar and consistent with confidence intervals of effect sizes overlapping. There was no important indication of inconsistency between direct and network meta-analysis results. The most commonly reported adverse events across all drugs were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness and rash or skin disorders; however, reporting of adverse events was highly variable across AEDs and across studies.

Authors' conclusions: High-certainty evidence demonstrates that for people with focal onset seizures, current first-line treatment options carbamazepine and lamotrigine, as well as newer drug eventrate, show the best profile in terms of treatment failure and seizure control as first-line treatments. For people with generalised tonic-clonic seizures (with or without other seizure types), current first-line treatment sodium valproate has the best profile compared to all other treatments, but lamotrigine and eventrate would be the most suitable alternative first-line treatments, particularly for those for whom sodium valproate may not be an appropriate treatment option. Further evidence from randomised controlled trials recruiting individuals with generalised tonic-clonic seizures (with or without other seizure types) is needed.

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Movement Disorders Secondary to Novel Antiseizure Medications in Pediatric Populations: A Systematic Review and Meta-analysis of Risk

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Abstract

Novel antiseizure medications are thought to be safer than their conventional counterparts, though no dedicated analysis of movement disorder risk among pediatric populations using novel antiseizure medications has been completed. We report a systematic review with meta-analysis describing the relationship between novel antiseizure medications and movement disorders in pediatrics.MEDLINE, EMBASE, and the World Health Organization's

International Clinical Trials Registry Platform were searched up to October 2020 for randomized controlled trials investigating novel antiseizure medications in pediatric populations. Antiseizure medications included lacosamide, perampanel, eslicarbazepine, rufinamide, fenfluramine, cannabidiol, and brivaracetam. Outcomes were pooled using random effects models; risk difference (RD) and 95% confidence intervals (CIs) were calculated.Twenty-three studies were selected from 1690 nonredundant manuscripts (n = 1912 total). There was a significantly increased risk of movement disorders associated with perampanel (RD 0.07, 95% CI 0.01-0.13; n = 133), though only 1 relevant trial was found. No increased risk of movement disorders was found with other antiseizure medications.Our findings indicate most novel antiseizure medications are safe to use in pediatric populations with respect to movement disorders. However, findings were limited by quality of adverse event reporting.

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Rapid versus slow withdrawal of antiepileptic drugs

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Abstract

Background: The ideal objective of treating a person with epilepsy is to induce remission (free of seizures for some time) using antiepileptic drugs (AEDs) and withdraw the AEDs without causing seizure recurrence. Prolonged usage of AEDs may have long-term adverse effects. Hence, when a person with epilepsy is in remission, it is logical to attempt to discontinue the medication. The timing of withdrawal and the mode of withdrawal arise while contemplating withdrawal of AEDs. This review examines the evidence for the rate of withdrawal of AEDs (whether rapid or slow tapering) and its effect on seizure recurrence. This is an updated version of the Cochrane Review previously published in 2020.

Objectives: To quantify risk of seizure recurrence after rapid (tapering period of three months or less) or slow (tapering period of more than three months) discontinuation of antiepileptic drugs in adults and children with epilepsy who are in remission, and to assess which variables modify the risk of seizure recurrence.

Search methods: For the latest update, on 8 November 2021, we searched: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid), and SCOPUS. There were no language restrictions. CRS Web includes randomized or quasi-randomized, controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), CENTRAL, and the Specialized Registers of Cochrane Review Groups including Epilepsy.

Selection criteria: Randomized controlled trials that evaluated withdrawal of AEDs in a rapid or slow tapering after varying periods of seizure control in people with epilepsy.

Data collection and analysis: Two review authors independently assessed the trials for inclusion and extracted the data. The outcomes assessed included seizure freedom after one, two, or five years of AED withdrawal; time to recurrence of seizure following withdrawal; occurrence of status epilepticus; mortality; morbidity due to seizure, such as injuries, fractures, and aspiration pneumonia; and quality of life (assessed by validated scale).

Main results: There are two included studies in this review. One study randomized 57 children with epilepsy with seizure freedom for at least two years to taper down the AED over one or six months. The study was not blinded and there were no details of randomization.

Over the period of 54 months of follow-up, 20/30 participants in the one-month group remained seizure-free compared to 15/27 participants in the six-month group (no evidence of a difference). There was no information on time of seizure recurrence for each group to allow a comparison. The other study involved 149 children. There was a non-significant trend towards a lower risk of seizure recurrence after one year of AED withdrawal in participants allocated to slow tapering (risk ratio (RR) 0.76, 95% confidence interval (CI) 0.58 to 1.01; P = 0.06; very low-certainty evidence). At the end of two years, 30 participants were seizure free in the rapid-tapering group and 29 participants in the slow-tapering group (RR 0.87, 95% CI 0.58 to 1.29; P = 0.48; very low-certainty evidence). At the end of five years, 10 participants were seizure free in the rapid-tapering group and six participants in the slow-tapering group (RR 1.40, 95% CI 0.54 to 3.65; P = 0.49; very low-certainty evidence). There were no data for the other outcomes. Due to the methodological heterogeneity and the difference in the duration of tapering, we did not perform a quantitative synthesis of these studies. Currently, one Italian trial is ongoing that is investigating if a slow or a rapid withdrawal schedule of AEDs influences return of seizures (relapse) in adults with focal or generalized epilepsy who have been seizure free for at least two years (no preliminary results available).
Authors' conclusions: In view of methodological deficiencies, and small sample size of the two included studies, we cannot draw any reliable conclusions regarding the optimal rate of tapering of AEDs. Using GRADE, we assessed the certainty of the evidence as very low for outcomes for which data were available. We judged both studies to be at an overall high risk of bias. Further studies are needed in adults and children to investigate the optimal rate of withdrawal of AEDs and to study the effects of variables such as seizure types, aetiology, intellectual disability, electroencephalography abnormalities, presence of neurological deficits, and other comorbidities on the rate of tapering.

Fever

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Prophylactic drug management for febrile seizures in children
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Abstract
Background: Febrile seizures occurring in a child older than one month during an episode of fever affect 2-4% of children in Great Britain and the United States and recur in 30%. Rapid-acting antiepileptics and antipyretics given during subsequent fever episodes have been used to avoid the adverse effects of continuous antiepileptic drugs. This is an updated version of a Cochrane Review previously published in 2017.
Objectives: To evaluate primarily the effectiveness and safety of antiepileptic and antipyretic drugs used prophylactically to treat children with febrile seizures; and also to evaluate any other drug intervention where there is a sound biological rationale for its use.
Search methods: For the latest update we searched the following databases on 3 February 2020: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 31 January 2020). CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the

specialised registers of Cochrane Review Groups including the Cochrane Epilepsy Group. We imposed no language restrictions and contacted researchers to identify continuing or unpublished studies.
Selection criteria: Trials using randomised or quasi-randomised participant allocation that compared the use of antiepileptics, antipyretics or recognised Central Nervous System active agents with each other, placebo, or no treatment.
Data collection and analysis: For the original review, two review authors independently applied predefined criteria to select trials for inclusion and extracted the predefined relevant data, recording methods for randomisation, blinding, and exclusions. For the 2016 update, a third review author checked all original inclusions, data analyses, and updated the search. For the 2020 update, one review author updated the search and performed the data analysis following a peer-review process with the original review authors. We assessed seizure recurrence at 6, 12, 18, 24, 36, 48 months, and where data were available at age 5 to 6 years along with recorded adverse effects. We evaluated the presence of publication bias using funnel plots.
Main results: We included 42 articles describing 32 randomised trials, with 4431 randomised participants used in the analysis of this review. We analysed 15 interventions of continuous or intermittent prophylaxis and their control treatments. Methodological quality was moderate to poor in most studies. We found no significant benefit for intermittent phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen, or zinc sulfate versus placebo or no treatment; nor for diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo; nor for continuous phenobarbital versus diazepam, intermittent rectal diazepam versus intermittent valproate, or oral diazepam versus clobazam. There was a significant reduction of recurrent febrile seizures with intermittent diazepam versus placebo or no treatment at six months (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.48 to 0.85; 6 studies, 1151 participants; moderate-certainty evidence), 12 months (RR 0.69, 95% CI 0.56 to 0.84; 8 studies, 1416 participants; moderate-certainty evidence), 18 months (RR 0.37, 95% CI 0.23 to 0.60; 1 study, 289 participants; low-certainty evidence), 24 months (RR 0.73, 95% CI 0.56 to 0.95; 4 studies, 739 participants; high-certainty evidence), 36 months (RR 0.58, 95% CI 0.40 to 0.85; 1 study, 139 participants; low-certainty evidence), 48 months (RR 0.36, 95% CI 0.15 to 0.89; 1 study, 110 participants; moderate-certainty evidence), with no benefit at 60 to 72 months (RR 0.08, 95% CI 0.00 to 1.31; 1 study, 60 participants; very low-certainty evidence). Phenobarbital versus placebo or no treatment reduced seizures at six months (RR 0.59, 95% CI 0.42 to 0.83; 6 studies, 833 participants; moderate-certainty evidence), 12 months (RR 0.54, 95% CI 0.42 to 0.70; 7 studies, 807 participants; low-certainty evidence), and 24 months (RR 0.69, 95% CI 0.53 to 0.89; 3 studies, 533 participants; moderate-certainty evidence), but not at 18 months (RR 0.77, 95% CI 0.56 to 1.05; 2 studies, 264 participants) or 60 to 72 months follow-up (RR 1.50, 95% CI 0.61 to 3.69; 1 study, 60 participants; very low-certainty evidence). Intermittent clobazam compared to placebo at six months resulted in a RR of 0.36 (95% CI 0.20 to 0.64; 1 study, 60 participants; low-certainty evidence), an effect found against an extremely high (83.3%) recurrence rate in the controls, a result that needs replication. When compared to intermittent diazepam, intermittent oral melatonin did not significantly reduce seizures at six months (RR 0.45, 95% CI 0.18 to 1.15; 1 study, 60 participants; very-low certainty evidence). When compared to placebo, intermittent oral levetiracetam significantly reduced recurrent seizures at 12 months (RR 0.27, 95% CI 0.15 to 0.52; 1 study, 115 participants; very low-certainty evidence). The recording of adverse effects was variable. Two studies reported lower comprehension scores in phenobarbital-treated

children. Adverse effects were recorded in up to 30% of children in the phenobarbital-treated groups and 36% in benzodiazepine-treated groups. We found evidence of publication bias in the meta-analyses of comparisons for phenobarbital versus placebo (seven studies) at 12 months but not at six months (six studies); and valproate versus placebo (four studies) at 12 months. There were too few studies to identify publication bias for the other comparisons. The methodological quality of most of the included studies was low or very low. Methods of randomisation and allocation concealment often did not meet current standards, and 'treatment versus no treatment' was more commonly seen than 'treatment versus placebo', leading to obvious risks of bias. AUTHORS' CONCLUSIONS: We found reduced recurrence rates for intermittent diazepam and continuous phenobarbital, with adverse effects in up to 30% of children. The apparent benefit for clobazam treatment in one trial needs to be replicated. Levetiracetam also shows benefit with a good safety profile; however, further study is required. Given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon.

Fluid management

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Balanced Versus Unbalanced Fluid in Critically Ill Children: Systematic Review and Meta-Analysis

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Abstract

Objectives: The ideal crystalloid fluid bolus therapy for fluid resuscitation in children remains unclear, but pediatric data are limited. Administration of 0.9% saline has been associated with hyperchloremic metabolic acidosis and acute kidney injury. The primary objective of this systematic review was to compare the effect of balanced versus unbalanced fluid bolus therapy on the mean change in serum bicarbonate or pH within 24 hours in critically ill children.

Data sources: We searched MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, CENTRAL Trials Registry of the Cochrane Collaboration, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform.

Study selection: Using the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols guidelines, we retrieved all controlled trials and observational cohort studies comparing balanced and unbalanced resuscitative fluids in critically ill children. The primary outcome was the change in serum bicarbonate or blood pH. Secondary outcomes included the prevalence of hyperchloremia, acute kidney injury, renal replacement therapy, and mortality.

Data extraction: Study screening, inclusion, data extraction, and risk of bias assessments were performed independently by two authors.

Data synthesis: Among 481 references identified, 13 met inclusion criteria. In the meta-analysis of three randomized controlled trials with a population of 162 patients, we found a greater mean change in serum bicarbonate level (pooled estimate 1.60 mmol/L; 95% CI, 0.04-3.16; p = 0.04) and pH level (pooled mean difference 0.03; 95% CI, 0.00-0.06; p = 0.03) after 4-12 hours of rehydration with balanced versus unbalanced fluids. No differences were found in chloride serum level, acute kidney injury, renal replacement therapy, or mortality. **Conclusions:** Our systematic review found some evidence of improvement in blood pH and bicarbonate values in critically ill children after 4-12 hours of fluid bolus therapy with balanced fluid compared with the unbalanced fluid. However, a randomized controlled trial is needed to establish whether these findings have an impact on clinical outcomes before recommendations can be generated.

Health promotion

Front Public Health. 2021 Aug 19;9:671782.
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Moderate-to-Vigorous Physical Activity Is Associated With Cardiorespiratory Fitness Among Primary Schoolchildren Living in Côte d'Ivoire, South Africa, and Tanzania
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Abstract
Background: Physical inactivity and low cardiorespiratory fitness (CRF) are independent cardiovascular risk factors among children, but have rarely been investigated concurrently in sub-Saharan Africa. The purpose of this study was to compare physical activity (PA) and CRF of primary schoolchildren living in Côte d'Ivoire (CI), South Africa (ZA), and Tanzania (TZ), to test sex- and age-related differences, and to examine whether PA and CRF are associated with each other. **Methods:** Baseline data from an ongoing cluster-randomized controlled trial were used, including 499 children from CI (Taabo, 49% girls, *M* = 8.0 ± 1.6 years), 1,074 children from ZA (Gqeberha, 49% girls, *M* = 8.3 ± 1.4 years), and 593 children from TZ (Ifakara, 51% girls, *M* = 9.4 ± 1.7 years). PA was assessed by accelerometry and CRF by a 20 m shuttle-run test. The data were analyzed using multi-/univariate analyses of variance and mixed linear models. **Results:** Most children met recommendations put forward by the World Health Organization for moderate-to-vigorous PA (MVPA) and achieved high CRF scores. In CI, 89.6% of the children met MVPA recommendations (boys: 91.7%, girls: 87.4%), whereas this rate was 76.9% in ZA (boys: 91.0%, girls: 62.4%), and 93.8% in TZ (boys: 95.5%, girls: 92.0%). Children from TZ had the highest CRF and MVPA levels, followed by children from CI and ZA. Boys had higher MVPA levels than girls, whereas girls engaged in more sedentary behavior. Sex differences were strongest in ZA. Sedentary behavior and MVPA were higher among older schoolchildren compared to their younger peers. Higher MVPA, but not sedentary behavior, was associated with better CRF. **Conclusions:** In all three settings, higher levels of MVPA

were associated with higher CRF scores. Nevertheless, children living in the most urbanized setting (such as observed in ZA) were physically less active and had lower CRF than peers living in more rural areas (such as observed in CI and TZ). Particularly for girls, urbanization might increase the risk for insufficient MVPA, which may have negative effects on their CRF, thus negatively influencing health and well-being at later age.

Hygiene, sanitation and environmental health

Indoor air pollution

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Prenatal and Postnatal Household Air Pollution Exposures and Pneumonia Risk: Evidence From the Ghana Randomized Air Pollution and Health Study

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Abstract

Background: Nearly 40% of the world's population is exposed daily to household air pollution. The relative impact of prenatal and postnatal household air pollution exposure on early childhood pneumonia, a leading cause of mortality, is unknown.

Research question: Are prenatal or postnatal household air pollution, or both, associated with pneumonia risk in the first year of life?

Study design and methods: The Ghana Randomized Air Pollution and Health Study enrolled 1,414 nonsmoking, pregnant women before 24 weeks' gestation with prospective follow-up to the child's age of 1 year. We measured 72-h personal household air pollution exposures, indexed by carbon monoxide (CO), four times prenatally and three times postnatally. Weekly fieldworker surveillance identified ill-appearing children for physician pneumonia assessment. We used quasi-Poisson models to examine associations between prenatal and postnatal CO and physician-diagnosed pneumonia and severe pneumonia. Sex-specific effects were examined.

Results: Of the 1,306 live births, 1,141 infants were followed up with 55,605 child-weeks of fieldworker surveillance. The estimated risk for pneumonia and severe pneumonia in the first year of life increased by 10% (relative risk [RR], 1.10; 95% CI, 1.04-1.16) and 15% (RR, 1.15; 95% CI, 1.03-1.28), respectively, per 1-part per million (ppm) increase in average prenatal CO exposure and by 6% (RR, 1.06; 95% CI, 0.99-1.13) per 1-ppm increase in average postnatal CO exposure. Sex-stratified analyses suggest that in girls, higher prenatal CO exposure was associated with pneumonia risk, while no association was seen in boys.

Interpretation: Prenatal household air pollution exposure increased risk of pneumonia and severe pneumonia in the first year of life. Clean-burning interventions may be most effective when begun prenatally.

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Portable HEPA filter air cleaner use during pregnancy and children's body mass index at two years of age: The UGAAR randomized controlled trial

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Abstract

Importance: Gestational exposure to particulate matter (PM) air pollution may increase the risk of childhood obesity, but the impact of reducing air pollution during pregnancy on obesity-related outcomes in childhood has not been examined.

Objective: To assess the impact of reducing gestational PM exposure on body mass index (BMI) at two years of age.

Methods: In this single-blind, parallel group randomized controlled trial in Ulaanbaatar Mongolia, we randomly assigned 540 pregnant women to receive 1-2 portable high efficiency particulate air (HEPA) filter air cleaners or no air cleaners. We measured height and weight when children were a mean age of 23.8 months. Our primary outcome was age- and sex-specific BMI z-score based on the World Health Organization 2007 Growth Charts. Secondary outcomes included age- and sex-specific weight z score, overweight/obesity (defined as BMI z-score > 2.00), and catch-up growth (defined using various cut-offs to identify children with relatively low birth weight for sex and gestational age and relatively high age- and sex-specific weight in childhood). We imputed missing outcome data using multiple imputation with chained equations and our primary analysis was by intention to treat (ITT). We estimated intervention effects on continuous and binary outcomes using linear and logistic regression, respectively.

Results: After excluding known miscarriages, still births, and neonatal deaths our analysis included 480 children (235 control and 245 intervention). The mean (SD) child BMI z score was 0.79 (1.0); 9.8% of children were overweight or obese. The mean BMI z score of children who were randomly assigned to the intervention group was 0.16-units lower (95% CI: -0.35, 0.04) than children in the control group. The intervention was also associated with reductions in overweight/obesity (odds ratio = 0.59; 95% CI: 0.31, 1.12). Catch-up growth occurred less frequently in the intervention group, but effect estimates varied depending on the specific definition of catch-up growth and confidence intervals consistently spanned no effect.

Conclusions: We found that the use of portable air cleaners during pregnancy was associated with improvements in obesity-related outcomes, although some effect estimates lacked precision. Reducing PM exposure during pregnancy may lead to improvements in cardiometabolic health in childhood.

Water, Sanitation and Hygiene

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The Impact of Pro-Poor Sanitation Subsidies in Open Defecation-Free Communities: A Randomized, Controlled Trial in Rural Ghana

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Abstract

Background: According to the World Health Organization/United Nations International Children's Fund Joint Monitoring Program, 494million494million people practice open defecation globally. After achieving open defecation-free (ODF) status through efforts such as Community-Led Total Sanitation (CLTS), communities (particularly vulnerable households) may revert to open defecation, especially when toilet collapse is common and durable toilets are unaffordable. Accordingly, there is increasing interest in pro-poor sanitation subsidies.

Objectives: This study determined the impacts of a pro-poor sanitation subsidy program on sanitation conditions among the most vulnerable households and others in the community.

Methods: In 109 post-ODF communities in Northern Ghana, we conducted a cluster randomized controlled trial to evaluate a pro-poor subsidy program that identified the most vulnerable households through community consultation to receive vouchers for durable toilet substructures. We surveyed households to assess toilet coverage, quality, and use before and after the intervention and tracked program costs.

Results: Overall, sanitation conditions deteriorated substantially from baseline to endline (average of 21 months). In control communities (not receiving the pro-poor subsidy), open defecation increased from 25% (baseline) to 69% (endline). The subsidy intervention attenuated this deterioration (open defecation increased from 25% to only 54% in subsidy communities), with the greatest impacts among voucher-eligible households. Noneligible households in compounds with subsidized toilets also exhibited lower open defecation levels owing to in-compound sharing (common in this context). CLTS followed by the subsidy program would benefit more households than CLTS alone but would cost 21-37% more per household that no longer practiced open defecation or upgraded to a durable toilet.

Discussion: Sanitation declines, often due to toilet collapse, suggest a need for approaches beyond CLTS alone. This subsidy program attenuated declines, but durable toilets likely remained unaffordable for noneligible households. Targeting criteria more closely aligned with sanitation inequities, such as household heads who are female or did not complete primary education, may help to generate greater and more sustainable impacts in Northern Ghana and, potentially, other contexts facing toilet collapse and limited market access.
https://doi.org/10.1289/EHP10443.

HIV / AIDS

Antiretroviral therapy (ART)

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Development of Dolutegravir Single-entity and Fixed-dose Combination Formulations for Children

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Abstract

Background: The World Health Organization (WHO) 2019 antiretroviral treatment guidelines recommend use of optimal treatment regimens in all populations. Dolutegravir-based regimens are the preferred first-line and second-line treatment in infants and children with HIV 4 weeks of age and above. There is an urgent need for optimal pediatric formulations of dolutegravir as single-entity (SE) and fixed-dose combination (FDC) to ensure correct dosing and adherence for swallowing and palatability. This article outlines the chronology of dolutegravir pediatric formulation development as granules and conventional and dispersible tablets in a total of 5 pharmacokinetic studies evaluating the relative bioavailability of dolutegravir SE and FDC formulations in healthy adults.

Methods: The relative bioavailability studies were 2-part, Phase I, open-label, randomized studies in healthy adults. Dolutegravir SE study compared conventional dolutegravir 50 and 25 mg with equivalent conventional 10-mg and dispersible 5-mg tablets, respectively. Subsequently, dolutegravir FDC study compared adult FDC of abacavir/dolutegravir/lamivudine and adult FDC of dolutegravir/lamivudine with their respective pediatric FDC formulations, taken as dispersion immediately or swallowed whole.

Results: As observed in previous studies, dolutegravir administered as dispersion (granules/dispersible tablets) showed relatively higher bioavailability compared with conventional tablets. The bioavailability of dolutegravir dispersible tablets (both SE and FDC) was approximately 1.6-fold higher when compared with conventional tablets. In addition, the bioavailability of abacavir/lamivudine was not impacted by dispersible formulation.

Conclusions: These studies demonstrate the successful development of pediatric dolutegravir-containing formulations as SE and FDC that permit pediatric dosing in line with WHO recommendations.

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Effect on growth of exposure to maternal antiretroviral therapy in breastmilk versus extended infant nevirapine prophylaxis among HIV-exposed perinatally uninfected infants in the PROMISE randomized trial

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Abstract

Background: Malnutrition is highly prevalent in HIV-exposed perinatally uninfected infants (HEUs) increasing the risk of morbidity and mortality throughout the life course. We set out to compare the effect of postnatal exposure to maternal antiretroviral therapy (mART) in breastmilk versus infant Nevirapine prophylaxis (iNVP) on somatic growth of HEUs in the randomized PROMISE trial.

Methods and findings: We randomized 2431 mothers with HIV and their 2444 HEUs from six African countries and India 6-14 days after delivery to mART or iNVP for prevention of breastmilk HIV transmission. The mART regimen contained tenofovir/emtricitabine (99%) plus lopinavir/ritonavir. Infant growth parameters were compared at postnatal week 10, 26, 74 and 104 using World Health Organization (WHO) z-scores for length-for-age (LAZ), weight-for-age (WAZ), and head circumference-for-age (HCAZ). Week 26 LAZ was the primary endpoint measure. Student T-tests compared mean LAZ, WAZ, and HCAZ; estimated mean and 95% confidence interval (CI) are presented. Maternal and infant baseline characteristics were comparable between study arms. The estimated median breastfeeding duration was 70 weeks. After a mean follow-up of 88 weeks, mean LAZ and WAZ were below the WHO reference population mean at all timepoints, whereas mean HCAZ was not. The mART and iNVP arms did not differ for the primary outcome measure of LAZ at week 26 (p-value = 0.39; estimated mean difference (95%CI) of -0.05 (-0.18, 0.07)) or any of the other secondary growth outcome measures or timepoints (all p-values≥0.16). Secondary analyses of the primary outcome measure adjusting for week 0 LAZ and other covariates did not change these results (all p-values≥0.09). However, infants assigned to mART were more likely to have stunting compared to iNVP infants at week 26 (odds ratio (95% CI): 1.28 (1.05, 1.57)).
Conclusions: In HEUs, growth effects from postnatal exposure to mART compared to iNVP were comparable for measures on length, weight and head circumference with no clinically relevant differences between the groups. Despite breastfeeding into the second year of life, length and weight were below reference population means at all ages in both arms. Further investment is needed to optimize postnatal growth of infants born to women with HIV.

N Engl J Med. 2021 Jul 22;385(4):330-341.
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Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV

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Abstract

Background: The World Health Organization recommends dolutegravir with two nucleoside reverse-transcriptase inhibitors (NRTIs) for second-line treatment of human immunodeficiency virus type 1 (HIV-1) infection. Evidence is limited for the efficacy of this regimen when NRTIs are predicted to lack activity because of drug resistance, as well as for the recommended switch of an NRTI from tenofovir to zidovudine.
Methods: In a two-by-two factorial, open-label, noninferiority trial, we randomly assigned patients for whom first-line therapy was failing (HIV-1 viral load, ≥1000 copies per milliliter) to receive dolutegravir or ritonavir-boosted darunavir and to receive tenofovir or zidovudine; all patients received lamivudine. The primary outcome was a week 48 viral load of less than 400 copies per milliliter, assessed with the Food and Drug Administration snapshot algorithm (noninferiority margin for the between-group difference in the percentage of patients with the primary outcome, 12 percentage points).
Results: We enrolled 464 patients at seven sub-Saharan African sites. A week 48 viral load of less than 400 copies per milliliter was observed in 90.2% of the patients in the dolutegravir

group (212 of 235) and in 91.7% of those in the darunavir group (210 of 229) (difference, -1.5 percentage points; 95% confidence interval [CI], -6.7 to 3.7; P = 0.58; indicating noninferiority of dolutegravir, without superiority) and in 92.3% of the patients in the tenofovir group (215 of 233) and in 89.6% of those in the zidovudine group (207 of 231) (difference, 2.7 percentage points; 95% CI, -2.6 to 7.9; P = 0.32; indicating noninferiority of tenofovir, without superiority). In the subgroup of patients with no NRTIs that were predicted to have activity, a viral load of less than 400 copies per milliliter was observed in more than 90% of the patients in the dolutegravir group and the darunavir group. The incidence of adverse events did not differ substantially between the groups in either factorial comparison.
Conclusions: Dolutegravir in combination with NRTIs was effective in treating patients with HIV-1 infection, including those with extensive NRTI resistance in whom no NRTIs were predicted to have activity. Tenofovir was noninferior to zidovudine as second-line therapy.

Diagnosis of HIV

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Point-of-care CD4 testing: Differentiated care for the most vulnerable
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Abstract
Background: South Africa, with the highest burden of HIV infection globally, has made huge strides in its HIV/ART programme, but AIDS deaths have not decreased proportionally to ART uptake. Advanced HIV disease (CD4 < 200 cells/mm^3) persists, and CD4 count testing is being overlooked since universal test-and-treat was implemented. Point-of-care CD4 testing could address this gap and assure differentiated care to these vulnerable patients with low CD4 counts.
Methods: A time randomised implementation trial was conducted, enrolling 603 HIV positive non-ART, not pregnant patients at a primary health care clinic in Durban, South Africa. Weeks were randomised to either point-of-care CD4 testing (n = 305 patients) or standard-of-care central laboratory CD4 testing (n = 298 patients) to assess the proportion initiating ART at 3 months. Cox regression, with robust standard errors adjusting for clustering by week, were used to assess the relationship between treatment initiation and arm.
Results: Among the 578 (299 point-of-care and 279 standard-of-care) patients eligible for analysis, there was no significant difference in the number of eligible patients initiating ART within 3 months in the point-of-care (73%) and the standard-of-care (68%) groups (*P* = 0.112). The time-to-treat analysis was not significantly different in patients with CD4 counts of 201-500 cells/mm^3 which could have been due to appointment scheduling to cope with the large burden of cases. However, in patients with advanced HIV disease (CD4 < 200cells/mm^3) 65% more patients started ART earlier in the point-of-care group (HR 1.65 (95% confidence interval (CI) = 0.99-2.75; *P* = 0.052) compared to the standard-of-care group.
Conclusions: Point-of-care testing decreased time-to-treatment in those with advanced HIV disease. With universal test and treat for HIV, rollout of simple point-of-care CD4 testing would ensure early diagnosis of advanced HIV disease and facilitate differentiated care for

these vulnerable patients as per the World Health Organisation 2020 target product profile for point-of-care CD4 testing.

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Effect of door-to-door distribution of HIV self-testing kits on HIV testing and antiretroviral therapy initiation: a cluster randomised trial in Malawi

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Abstract

Introduction: Reaching high coverage of HIV testing remains essential for HIV diagnosis, treatment and prevention. We evaluated the effectiveness and safety of door-to-door distribution of HIV self-testing (HIVST) kits in rural Malawi.

Methods: This cluster randomised trial, conducted between September 2016 and January 2018, used restricted 1:1 randomisation to allocate 22 health facilities and their defined areas to door-to-door HIVST alongside the standard of care (SOC) or the SOC alone. The study population included residents (≥16 years). HIVST kits were provided door-to-door by community-based distribution agents (CBDAs) for at least 12 months. The primary outcome was recent HIV testing (in the last 12 months) measured through an endline survey. Secondary outcomes were lifetime HIV testing and cumulative 16-month antiretroviral therapy (ART) initiations, which were captured at health facilities. Social harms were reported through community reporting systems. Analysis compared cluster-level outcomes by arm.

Results: Overall, 203 CBDAs distributed 273 729 HIVST kits. The endline survey included 2582 participants in 11 HIVST clusters and 2908 participants in 11 SOC clusters. Recent testing was higher in the HIVST arm (68.5%, 1768/2582) than the SOC arm (48.9%, 1422/2908), with adjusted risk difference (RD) of 16.1% (95% CI 6.5% to 25.7%). Lifetime testing was also higher in the HIVST arm (86.9%, 2243/2582) compared with the SOC arm (78.5%, 2283/2908; adjusted RD 6.3%, 95% CI 2.3% to 10.3%). Differences were most pronounced for adolescents aged 16-19 years (adjusted RD 18.6%, 95% CI 7.3% to 29.9%) and men (adjusted RD 10.2%, 95% CI 3.1% to 17.2%). Cumulative incidence of ART initiation was 1187.2 and 909.0 per 100 000 population in the HIVST and SOC arms, respectively (adjusted RD 309.1, 95% CI -95.5 to 713.7). Self-reported HIVST use was 42.5% (1097/2582), with minimal social harms reported.

Conclusion: Door-to-door HIVST increased recent and lifetime testing at population level and showed high safety, underscoring potential for HIVST to contribute to HIV elimination goals in priority settings.

HIV-TB coinfection

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What is the optimum time to start antiretroviral therapy in people with HIV and tuberculosis coinfection? A systematic review and meta-analysis

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Abstract

Background: HIV and tuberculosis are frequently diagnosed concurrently. In March 2021, World Health Organization recommended that antiretroviral therapy (ART) should be started within two weeks of tuberculosis treatment start, at any CD4 count. We assessed whether earlier ART improved outcomes in people with newly diagnosed HIV and tuberculosis.

Methods: We did a systematic review by searching nine databases for trials that compared earlier ART to later ART initiation in people with HIV and tuberculosis. We included studies published from database inception to 12 March 2021. We compared ART within four weeks versus ART more than four weeks after TB treatment, and ART within two weeks versus ART between two and eight weeks, and stratified analysis by CD4 count. The main outcome was death; secondary outcomes included IRIS and AIDS-defining events. We pooled effect estimates using random effects meta-analysis.

Results and discussion: We screened 2468 abstracts, and identified nine trials. Among people with all CD4 counts, there was no difference in mortality by earlier ART (≤4 week) versus later ART (>4 week) (risk difference [RD] 0%, 95% confidence interval [CI] -2% to +1%). Among people with CD4 count ≤50 cells/mm^3 , earlier ART (≤4 weeks) reduced risk of death (RD -6%, -10% to -1%). Among people with all CD4 counts earlier ART (≤4 weeks) increased the risk of IRIS (RD +6%, 95% CI +2% to +10%) and reduced the incidence of AIDS-defining events (RD -2%, 95% CI -4% to 0%). Results were similar when trials were restricted to the four trials which permitted comparison of ART within two weeks to ART between two and eight weeks. Trials were conducted between 2004 and 2014, before recommendations to treat HIV at any CD4 count or to rapidly start ART in people without TB. No trials included children or pregnant women. No trials included integrase inhibitors in ART regimens.

Discussion: Earlier ART did not alter risk of death overall among people living with HIV who had TB disease. For logistical and patient preference reasons, earlier ART initiation for everyone with TB and HIV may be preferred to later ART.

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

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Adverse perinatal outcomes associated with timing of initiation of antiretroviral therapy: Systematic review and meta-analysis

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Abstract

Background: The World Health Organization (WHO) recommends immediate initiation of lifelong antiretroviral therapy (ART) for all people living with HIV, including pregnant women. As a result, an increasing number of women living with HIV conceive while taking ART, the vast majority of whom reside in low- and middle-income countries (LMICs). We aimed to assess the association between timing of ART initiation and perinatal outcomes.
Methods: We conducted a systematic literature review by searching PubMed, CINAHL (EBSCOhost), Global Health (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials and four clinical trial databases (WHO International Clinical Trials Registry Platform, the Pan African Clinical Trials Registry, the ClinicalTrials.gov database, and the ISRCTN Registry) from 1 January 1980 to 28 April 2018. We identified studies reporting specific perinatal outcomes among pregnant women living with HIV according to timing of ART initiation and extracted data. Perinatal outcomes assessed were preterm birth (<37 weeks), very preterm birth (<32 weeks), low birthweight (<2500 g), very low birthweight (<1500 g), small for gestational age (<10th centile), very small for gestational age (<3rd centile) and neonatal death (<29 days). Random-effects meta-analyses examined perinatal outcomes associated with preconception and antenatal ART initiation as well as according to trimesters of antenatal initiation. We performed quality assessments and subgroup and sensitivity analyses, and assessed the effect of adjustment for confounders. This systematic review and meta-analyses is registered with PROSPERO, number CRD42021248987.
Results: Of 51 874 unique citations, 25 studies (eight prospective and 17 retrospective cohort studies) were eligible for analysis, including 40 920 women living with HIV. Preconception ART initiation was associated with a significantly increased risk of preterm birth (relative risk 1.16; 95% confidence interval [CI] 1.03-1.31) compared with antenatal ART initiation. Preconception ART initiation was not significantly associated with very preterm birth, low birthweight, very low birthweight, small for gestational age, very small for gestational age, or neonatal death. First trimester exposure (i.e. preconception or first trimester initiation) was not significantly associated with any increased risk of adverse perinatal outcomes. No significant association between timing of ART initiation and adverse perinatal outcomes was found in the studies of higher quality and those conducted in LMICs.
Conclusion: Preconception ART initiation is associated with preterm birth but no other adverse perinatal outcomes. In LMICs, where most pregnant women living with HIV reside, the timing of ART initiation was not associated with any adverse perinatal outcomes.

Helminth and other gastrointestinal disorders

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

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Soil-transmitted helminth infections and nutritional indices among Filipino schoolchildren

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Li[5,6], Archie C A Clements[7], Peter Steinmann[8,9], Kate Halton[10], Donald E Stewart[1,11], Donald P McManus[5], Darren J Gray[1]

Abstract

Background: Soil-transmitted helminth (STH) infections are still prevalent among schoolchildren in the Philippines. We evaluated the risk factors associated with STH and the relationship between STH and nutritional indices among schoolchildren aged 9-10 years in Laguna province, the Philippines.

Methods: We used the baseline data from 40 schools enrolled in a randomised controlled trial of the Magic Glasses Philippines health education package. Data on demographic and socio-economic variables, and STH related knowledge, attitudes and practices, were obtained through a questionnaire. Stool samples were collected and assessed for STH egg presence using the Kato-Katz technique. Haemoglobin levels and height and weight of study participants were also determined. The generalized estimating equations approach was used to construct logistic regression models to assess STH-associated risk factors, and the association between any STH infection and anaemia, child stunting, wasting and being underweight. The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616000508471).

Findings: Among 1,689 schoolchildren, the prevalence of any STH was 23%. The prevalence of anaemia, stunting, being underweight and wasting was 13%, 20.2%, 19% and 9.5%, respectively. Age, socio-economic status, rural/urban classification of schools and knowledge of STH were significant risk factors for acquiring a STH infection. Moreover, infections with any STH were significantly associated with stunting (P = <0.001) and being underweight (P = <0.003), but not wasting (P = 0.375) or anaemia (P = 0.462) after controlling for confounding covariates.

Conclusion: The study findings emphasise the need for sustainable deworming in tandem with other measures such as the provision of health education, improvements in sanitation and hygiene, and nutritional programs in order to control STH infections and improve morbidity outcomes in schoolchildren.

Malaria

Insecticide-treated bed nets and other materials

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Evaluation of the efficacy of insecticide-treated scarves to protect children from the trachoma vector *Musca sorbens* (Diptera: Muscidae): A phase II randomised controlled trial in Oromia, Ethiopia

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Abstract
Background: The eye-seeking fly *Musca sorbens* can act as a vector for ocular *Chlamydia trachomatis*, causing trachoma, yet there has been very little research on control measures. We investigated whether insect repellent products, specifically insecticide-treated clothing, could provide personal protection to the user from eye-seeking flies.
Methods: We first conducted a series of phase I laboratory studies to inform our choice of field intervention. We then conducted a phase II randomised controlled trial testing the efficacy of permethrin-treated scarves (PTS) in reducing fly-face contact in Oromia, Ethiopia. Children aged 4-10 years in full health and with no known adverse reactions to permethrin or other insecticides were allocated to either arm using restricted randomisation. Intervention arm children wore Insect Shield® versatile wraps (as PTS) for 28 days. The primary outcomes, fly-eye, -nose and -mouth contact, were assessed on the first day (0/30/60/180 minutes), on day 7 and on day 28. All participants present per timepoint were included in analyses. This trial was registered with ClinicalTrials.gov (NCT03813069).
Findings: Participants were recruited to the field trial between 29/10/2019 and 01/11/2019, 58 were randomised to test or control arm. More fly (-eye, -nose and -mouth) contacts were observed in the PTS arm at baseline. After adjusting for baseline contact rates, across all timepoints there was a 35% decrease in fly-eye contacts in the PTS relative to control arm (rate ratio [RR] 0.65, 95% CI 0.52-0.83). Similar cross-timepoint reductions were seen for fly-nose and fly-mouth contacts (RR 0.69, 95% CI 0.51-0.92 and RR 0.79, 95% CI 0.62-1.01, respectively). All children were included on day 0. Two in the control arm were absent on day 7, one left the study and four were excluded from analysis at day 28. No adverse events occurred in the trial.
Interpretation: *Musca sorbens* flies are sufficiently repelled by PTS to reduce fly-eye contacts for the wearer, thus possibly reducing the risk of trachoma transmission. Permethrin-treated scarves may therefore an alternative to insecticide space spraying for protection from these flies.

Intermittent preventative treatment and seasonal malaria prophylaxis

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Effectiveness of seasonal malaria chemoprevention (SMC) treatments when SMC is implemented at scale: Case-control studies in 5 countries
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Abstract
Background: Seasonal malaria chemoprevention (SMC) has shown high protective efficacy against clinical malaria and severe malaria in a series of clinical trials. We evaluated the

effectiveness of SMC treatments against clinical malaria when delivered at scale through national malaria control programmes in 2015 and 2016.
Methods and findings: Case-control studies were carried out in Mali and The Gambia in 2015, and in Burkina Faso, Chad, Mali, Nigeria, and The Gambia in 2016. Children aged 3-59 months presenting at selected health facilities with microscopically confirmed clinical malaria were recruited as cases. Two controls per case were recruited concurrently (on or shortly after the day the case was detected) from the neighbourhood in which the case lived. The primary exposure was the time since the most recent course of SMC treatment, determined from SMC recipient cards, caregiver recall, and administrative records. Conditional logistic regression was used to estimate the odds ratio (OR) associated with receipt of SMC within the previous 28 days, and SMC 29 to 42 days ago, compared with no SMC in the past 42 days. These ORs, which are equivalent to incidence rate ratios, were used to calculate the percentage reduction in clinical malaria incidence in the corresponding time periods. Results from individual countries were pooled in a random-effects meta-analysis. In total, 2,126 cases and 4,252 controls were included in the analysis. Across the 7 studies, the mean age ranged from 1.7 to 2.4 years and from 2.1 to 2.8 years among controls and cases, respectively; 42.2%-50.9% and 38.9%-46.9% of controls and cases, respectively, were male. In all 7 individual case-control studies, a high degree of personal protection from SMC against clinical malaria was observed, ranging from 73% in Mali in 2016 to 98% in Mali in 2015. The overall OR for SMC within 28 days was 0.12 (95% CI: 0.06, 0.21; $p < 0.001$), indicating a protective effectiveness of 88% (95% CI: 79%, 94%). Effectiveness against clinical malaria for SMC 29-42 days ago was 61% (95% CI: 47%, 72%). Similar results were obtained when the analysis was restricted to cases with parasite density in excess of 5,000 parasites per microlitre: Protective effectiveness 90% (95% CI: 79%, 96%; P<0.001), and 59% (95% CI: 34%, 74%; P<0.001) for SMC 0-28 days and 29-42 days ago, respectively. Potential limitations include the possibility of residual confounding due to an association between exposure to malaria and access to SMC, or differences in access to SMC between patients attending a clinic and community controls; however, neighbourhood matching of cases and controls, and covariate adjustment, attempted to control for these aspects, and the observed decline in protection over time, consistent with expected trends, argues against a major bias from these sources.
Conclusions: SMC administered as part of routine national malaria control activities provided a very high level of personal protection against clinical malaria over 28 days post-treatment, similar to the efficacy observed in clinical trials. The case-control design used in this study can be used at intervals to ensure SMC treatments remain effective.

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Intermittent preventive treatment for malaria in infants
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Abstract
Background: Intermittent preventive treatment could help prevent malaria in infants (IPTi) living in areas of moderate to high malaria transmission in sub-Saharan Africa. The World Health Organization (WHO) policy recommended IPTi in 2010, but its adoption in countries has been limited.

Objectives: To evaluate the effects of intermittent preventive treatment (IPT) with antimalarial drugs to prevent malaria in infants living in malaria-endemic areas.
Search methods: We searched the following sources up to 3 December 2018: the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (the Cochrane Library), MEDLINE (PubMed), Embase (OVID), LILACS (Bireme), and reference lists of articles. We also searched the metaRegister of Controlled Trials (mRCT) and the WHO International Clinical Trials Registry Platform (ICTRP) portal for ongoing trials up to 3 December 2018.
Selection criteria: We included randomized controlled trials (RCTs) that compared IPT to placebo or no intervention in infants (defined as young children aged between 1 to 12 months) in malaria-endemic areas.
Data collection and analysis: The primary outcome was clinical malaria (fever plus asexual parasitaemia). Two review authors independently assessed trials for inclusion, evaluated the risk of bias, and extracted data. We summarized dichotomous outcomes and count data using risk ratios (RR) and rate ratios respectively, and presented all measures with 95% confidence intervals (CIs). We extracted protective efficacy values and their 95% CIs; when an included trial did not report this data, we calculated these values from the RR or rate ratio with its 95% CI. Where appropriate, we combined data in meta-analyses and assessed the certainty of the evidence using the GRADE approach.
Main results: We included 12 trials that enrolled 19,098 infants; all were conducted in sub-Saharan Africa. Three trials were cluster-RCTs. IPTi with sulfadoxine-pyrimethamine (SP) was evaluated in 10 trials from 1999 to 2013 (n = 15,256). Trials evaluating ACTs included dihydroartemisinin-piperaquine (1 trial, 147 participants; year 2013), amodiaquine-artesunate (1 study, 684 participants; year 2008), and SP-artesunate (1 trial, 676 participants; year 2008). The earlier studies evaluated IPTi with SP, and were conducted in Tanzania (in 1999 and 2006), Mozambique (2004), Ghana (2004 to 2005), Gabon (2005), Kenya (2008), and Mali (2009). One trial evaluated IPTi with amodiaquine in Tanzania (2000). Later studies included three conducted in Kenya (2008), Tanzania (2008), and Uganda (2013), evaluating IPTi in multiple trial arms that included artemisinin-based combination therapy (ACT). Although the effect size varied over time and between drugs, overall IPTi impacts on the incidence of clinical malaria overall, with a 30% reduction (rate ratio 0.70, 0.62 to 0.80; 10 studies, 10,602 participants). The effect of SP appeared to attenuate over time, with trials conducted after 2009 showing little or no effect of the intervention. IPTi with SP probably resulted in fewer episodes of clinical malaria (rate ratio 0.78, 0.69 to 0.88; 8 trials, 8774 participants, moderate-certainty evidence), anaemia (rate ratio 0.82, 0.68 to 0.98; 6 trials, 7438 participants, moderate-certainty evidence), parasitaemia (rate ratio 0.66, 0.56 to 0.79; 1 trial, 1200 participants, moderate-certainty evidence), and fewer hospital admissions (rate ratio 0.85, 0.78 to 0.93; 7 trials, 7486 participants, moderate-certainty evidence). IPTi with SP probably made little or no difference to all-cause mortality (risk ratio 0.93, 0.74 to 1.15; 9 trials, 14,588 participants, moderate-certainty evidence). Since 2009, IPTi trials have evaluated ACTs and indicate impact on clinical malaria and parasitaemia. A small trial of DHAP in 2013 shows substantive effects on clinical malaria (RR 0.42, 0.33 to 0.54; 1 trial, 147 participants, moderate-certainty evidence) and parasitaemia (moderate-certainty evidence).
Authors' conclusions: In areas of sub-Saharan Africa, giving antimalarial drugs known to be effective against the malaria parasite at the time to infants as IPT probably reduces the risk of clinical malaria, anaemia, and hospital admission. Evidence from SP studies over a 19-year period shows declining efficacy, which may be due to increasing drug resistance. Combinations with ACTs appear promising as suitable alternatives for IPTi.

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Ivermectin treatment in humans for reducing malaria transmission

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Abstract

Background: Malaria is transmitted through the bite of Plasmodium-infected adult female Anopheles mosquitoes. Ivermectin, an anti-parasitic drug, acts by killing mosquitoes that are exposed to the drug while feeding on the blood of people (known as blood feeds) who have ingested the drug. This effect on mosquitoes has been demonstrated by individual randomized trials. This effect has generated interest in using ivermectin as a tool for malaria control.

Objectives: To assess the effect of community administration of ivermectin on malaria transmission.

Search methods: We searched the Cochrane Infectious Diseases Group (CIDG) Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, Science Citation index - expanded, the World Health Organization (WHO) International Clinical Trials Registry Platform, ClinicalTrials.gov, and the National Institutes of Health (NIH) RePORTER database to 14 January 2021. We checked the reference lists of included studies for other potentially relevant studies, and contacted researchers working in the field for unpublished and ongoing trials.

Selection criteria: We included cluster-randomized controlled trials (cRCTs) that compared ivermectin, as single or multiple doses, with a control treatment or placebo given to populations living in malaria-endemic areas, in the context of mass drug administration. Primary outcomes were prevalence of malaria parasite infection and incidence of clinical malaria in the community.

Data collection and analysis: Two review authors independently extracted data on the number of events and the number of participants in each trial arm at the time of assessment. For rate data, we noted the total time at risk in each trial arm. To assess risk of bias, we used Cochrane's RoB 2 tool for cRCTs. We documented the method of data analysis, any adjustments for clustering or other covariates, and recorded the estimate of the intra-cluster correlation (ICC) coefficient. We re-analysed the trial data provided by the trial authors to adjust for cluster effects. We used a Poisson mixed-effect model with small sample size correction, and a cluster-level analysis using the linear weighted model to adequately adjust for clustering. MAIN RESULTS: We included one cRCT and identified six ongoing trials. The included cRCT examined the incidence of malaria in eight villages in Burkina Faso, randomized to two arms. Both trial arms received a single dose of ivermectin 150 µg/kg to 200 µg/kg, together with a dose of albendazole. The villages in the intervention arm received an additional five doses of ivermectin, once every three weeks. Children were enrolled into an active cohort, in which they were repeatedly screened for malaria infection. The primary outcome was the cumulative incidence of uncomplicated malaria in a cohort of children aged five years and younger, over the 18-week study. We judged the study to be at high risk of bias, as the analysis did not account for clustering or correlation between participants in the same village. The study did not demonstrate an effect of Ivermectin on the cumulative incidence of uncomplicated malaria in the cohort of children over the 18-week study (risk ratio 0.86, 95% confidence interval (CI) 0.62 to 1.17; P = 0.2607; very low-certainty evidence).

Authors' conclusions: We are uncertain whether community administration of ivermectin has an effect on malaria transmission, based on one trial published to date.

Treatment of uncomplicated malaria

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doi: 10.1186/s12936-022-04050-8.

Efficacy of 3-day low dose quinine plus clindamycin versus artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Kenyan children (CLINDAQUINE): an open-label randomized trial

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Abstract

Background: The World Health Organization recommends quinine plus clindamycin as first-line treatment of malaria in the first trimester of pregnancy and as a second-line treatment for uncomplicated falciparum malaria when artemisinin-based drug combinations are not available. The efficacy of quinine plus clindamycin was compared with that of artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in children below 5 years of age.

Methods: An open-label, phase 3, randomized trial was conducted in western Kenya. Children aged 6-59 months with uncomplicated falciparum malaria were randomly assigned (1:1) via a computer-generated randomization list to receive 3 days of twice a day treatment with either oral quinine (20 mg/kg/day) plus clindamycin (20 mg/kg/day) or artemether-lumefantrine (artemether 20 mg, lumefantrine 120 mg) as one (for those weighing 5-14 kg) or two (for those weighing 15-24 kg) tablets per dose. The primary outcome was a PCR-corrected rate of adequate clinical and parasitological response (ACPR) on day 28 in the per-protocol population.

Results: Of the 384 children enrolled, 182/192 (94.8%) receiving quinine plus clindamycin and 171/192 (89.1%) receiving artemether-lumefantrine completed the study. The PCR-corrected ACPR rate was 44.0% (80 children) in the quinine plus clindamycin group and 97.1% (166 children) in the artemether-lumefantrine group (treatment difference - 53.1%, 95% CI - 43.5% to - 62.7%). At 72 h after starting treatment, 50.3% (94 children) in the quinine plus clindamycin group were still parasitaemic compared with 0.5% (1 child) in the artemether-lumefantrine group. Three cases of severe malaria were recorded as serious adverse events in the quinine plus clindamycin group.

Conclusions: The study found no evidence to support the use of a 3-day low dose course of quinine plus clindamycin in the treatment of uncomplicated falciparum malaria in children under 5 years of age in Kenya, where artemether-lumefantrine is still effective.

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doi: 10.1186/s12936-021-03935-4.

Efficacy of artesunate-amodiaquine and artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria in Madagascar, 2018

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Abstract

Background: Since 2005, artemisinin-based combination therapy (ACT) has been recommended to treat uncomplicated falciparum malaria in Madagascar. Artesunate-amodiaquine (ASAQ) and artemether-lumefantrine (AL) are the first- and second-line treatments, respectively. A therapeutic efficacy study was conducted to assess ACT efficacy and molecular markers of anti-malarial resistance.

Methods: Children aged six months to 14 years with uncomplicated falciparum malaria and a parasitaemia of 1000-100,000 parasites/μl determined by microscopy were enrolled from May-September 2018 in a 28-day in vivo trial using the 2009 World Health Organization protocol for monitoring anti-malarial efficacy. Participants from two communes, Ankazomborona (tropical, northwest) and Matanga (equatorial, southeast), were randomly assigned to ASAQ or AL arms at their respective sites. PCR correction was achieved by genotyping seven neutral microsatellites in paired pre- and post-treatment samples. Genotyping assays for molecular markers of resistance in the pfk13, pfcrt and pfmdr1 genes were conducted.

Results: Of 344 patients enrolled, 167/172 (97%) receiving ASAQ and 168/172 (98%) receiving AL completed the study. For ASAQ, the day-28 cumulative PCR-uncorrected efficacy was 100% (95% CI 100-100) and 95% (95% CI 91-100) for Ankazomborona and Matanga, respectively; for AL, it was 99% (95% CI 97-100) in Ankazomborona and 83% (95% CI 76-92) in Matanga. The day-28 cumulative PCR-corrected efficacy for ASAQ was 100% (95% CI 100-100) and 98% (95% CI 95-100) for Ankazomborona and Matanga, respectively; for AL, it was 100% (95% CI 99-100) in Ankazomborona and 95% (95% CI 91-100) in Matanga. Of 83 successfully sequenced samples for pfk13, no mutation associated with artemisinin resistance was observed. A majority of successfully sequenced samples for pfmdr1 carried either the NFD or NYD haplotypes corresponding to codons 86, 184 and 1246. Of 82 successfully sequenced samples for pfcrt, all were wild type at codons 72-76.

Conclusion: PCR-corrected analysis indicated that ASAQ and AL have therapeutic efficacies above the 90% WHO acceptable cut-off. No genetic evidence of resistance to artemisinin was observed, which is consistent with the clinical outcome data. However, the most common pfmdr1 haplotypes were NYD and NFD, previously associated with tolerance to lumefantrine.

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The cardiovascular effects of amodiaquine and structurally related antimalarials: An individual patient data meta-analysis

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Abstract

Background: Amodiaquine is a 4-aminoquinoline antimalarial similar to chloroquine that is used extensively for the treatment and prevention of malaria. Data on the cardiovascular effects of amodiaquine are scarce, although transient effects on cardiac electrophysiology (electrocardiographic QT interval prolongation and sinus bradycardia) have been observed. We conducted an individual patient data meta-analysis to characterise the cardiovascular effects of amodiaquine and thereby support development of risk minimisation measures to improve the safety of this important antimalarial.

Methods and findings: Studies of amodiaquine for the treatment or prevention of malaria were identified from a systematic review. Heart rates and QT intervals with study-specific heart rate correction (QTcS) were compared within studies and individual patient data pooled for multivariable linear mixed effects regression. The meta-analysis included 2,681 patients from 4 randomised controlled trials evaluating artemisinin-based combination therapies (ACTs) containing amodiaquine (n = 725), lumefantrine (n = 499), piperaquine (n = 716), and pyronaridine (n = 566), as well as monotherapy with chloroquine (n = 175) for uncomplicated malaria. Amodiaquine prolonged QTcS (mean = 16.9 ms, 95% CI: 15.0 to 18.8) less than chloroquine (21.9 ms, 18.3 to 25.6, p = 0.0069) and piperaquine (19.2 ms, 15.8 to 20.5, p = 0.0495), but more than lumefantrine (5.6 ms, 2.9 to 8.2, p < 0.001) and pyronaridine (-1.2 ms, -3.6 to +1.3, p < 0.001). In individuals aged ≥12 years, amodiaquine reduced heart rate (mean reduction = 15.2 beats per minute [bpm], 95% CI: 13.4 to 17.0) more than piperaquine (10.5 bpm, 7.7 to 13.3, p = 0.0013), lumefantrine (9.3 bpm, 6.4 to 12.2, p < 0.001), pyronaridine (6.6 bpm, 4.0 to 9.3, p < 0.001), and chloroquine (5.9 bpm, 3.2 to 8.5, p < 0.001) and was associated with a higher risk of potentially symptomatic sinus bradycardia (≤50 bpm) than lumefantrine (risk difference: 14.8%, 95% CI: 5.4 to 24.3, p = 0.0021) and chloroquine (risk difference: 8.0%, 95% CI: 4.0 to 12.0, p < 0.001). The effect of amodiaquine on the heart rate of children aged <12 years compared with other antimalarials was not clinically significant. Study limitations include the unavailability of individual patient-level adverse event data for most included participants, but no serious complications were documented.

Conclusions: While caution is advised in the use of amodiaquine in patients aged ≥12 years with concomitant use of heart rate-reducing medications, serious cardiac conduction disorders, or risk factors for torsade de pointes, there have been no serious cardiovascular events reported after amodiaquine in widespread use over 7 decades. Amodiaquine and structurally related antimalarials in the World Health Organization (WHO)-recommended dose regimens alone or in ACTs are safe for the treatment and prevention of malaria.

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Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria

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Abstract

Background: The World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) to treat uncomplicated Plasmodium falciparum malaria. Concerns about artemisinin resistance have led to global initiatives to develop new partner drugs to protect artemisinin derivatives in ACT. Pyronaridine-artesunate is a novel ACT.

Objectives: To evaluate the efficacy of pyronaridine-artesunate compared to alternative ACTs for treating people with uncomplicated P falciparum malaria, and to evaluate the safety of pyronaridine-artesunate and other pyronaridine treatments compared to alternative treatments.
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. We also searched ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the ISRCTN registry for ongoing or recently completed trials. The date of the last search was 27 October 2021.
Selection criteria: For the efficacy analysis, we included randomized controlled trials (RCTs) of pyronaridine-artesunate for treating uncomplicated P falciparum malaria. For the safety analysis, we included RCTs that used pyronaridine alone or in combination with any other antimalarials. In addition to these analyses, we conducted a separate systematic review summarizing data on safety from non-randomized studies (NRS) of any patient receiving pyronaridine (NRS safety review). DATA COLLECTION AND ANALYSIS: Two review authors independently extracted all data and assessed the certainty of the evidence. We meta-analysed data to calculate risk ratios (RRs) for treatment failures between comparisons, and for safety outcomes between and across comparisons.
Main results: We included 10 relevant RCTs. Seven RCTs were co-funded by Shin Poong Pharmaceuticals, and three were funded by government agencies. Efficacy analysis (RCTs) For the efficacy analysis, we identified five RCTs comprising 5711 participants. This included 4465 participants from 13 sites in Africa, and 1246 participants from five sites in Asia. The analysis included 541 children aged less than five years. Overall, pyronaridine-artesunate had a polymerase chain reaction (PCR)-adjusted treatment failure rate of less than 5%. We evaluated pyronaridine-artesunate versus the following. • Artemether-lumefantrine. Pyronaridine artesunate may perform better for PCR-adjusted failures at day 28 (RR 0.59, 95% confidence interval (CI) 0.26 to 1.31; 4 RCTs, 3068 participants, low-certainty evidence); for unadjusted failures at day 28 (RR 0.27, 95% CI 0.13 to 0.58; 4 RCTs, 3149 participants, low-certainty evidence); and for unadjusted failures at day 42 (RR 0.61, 95% CI 0.46 to 0.82; 4 RCTs, 3080 participants, low-certainty evidence). For PCR-adjusted failures at day 42, there may be little or no difference between groups (RR 0.86, 95% CI 0.49 to 1.51; 4 RCTs, 2575 participants, low-certainty evidence). • Artesunate-amodiaquine. Pyronaridine artesunate may perform better for PCR-adjusted failures at day 28 (RR 0.55, 95% CI 0.11 to 2.77; 1 RCT, 1245 participants, low-certainty evidence); probably performs better for unadjusted failures at day 28 (RR 0.49, 95% CI 0.30 to 0.81; 1 RCT, 1257 participants, moderate-certainty evidence); may make little or no difference for PCR-adjusted failures at day 42 (RR 0.98, 95% CI 0.20 to 4.83; 1 RCT, 1091 participants, low-certainty evidence); and probably makes little or no difference for unadjusted failures at day 42 (RR 0.98, 95% CI 0.78 to 1.23; 1 RCT, 1235 participants, moderate-certainty evidence). • Mefloquine plus artesunate. Pyronaridine artesunate may perform better for PCR-adjusted failures at day 28 (RR 0.37, 95% CI 0.13 to 1.05; 1 RCT, 1117 participants, low-certainty evidence); probably performs better for unadjusted failures at day 28 (RR 0.36, 95% CI 0.17 to 0.78; 1 RCT, 1120 participants, moderate-certainty evidence); may make little or no difference for unadjusted failures at day 42 (RR 0.84, 95% CI 0.54 to 1.31; 1 RCT, 1059 participants, low-certainty evidence); but may lead to higher PCR-adjusted failures at day 42 (RR 1.80, 95% CI 0.90 to 3.57; 1 RCT, 1037 participants, low-certainty evidence). Safety analysis (RCTs) For the RCT safety analysis, we identified eight RCTs, one of which was delineated by study site, comparing pyronaridine-

artesunate to other antimalarials. Pyronaridine-artesunate was associated with raised liver enzymes compared to other antimalarials: alanine aminotransferase (ALT) (RR 3.59, 95% CI 1.76 to 7.33; 8 RCTS, 6669 participants, high-certainty evidence) and aspartate transaminase (AST) (RR 2.22, 95% CI 1.12 to 4.41; 8 RCTs, 6669 participants, moderate-certainty evidence). No such effect was demonstrated with bilirubin (RR 1.03, 95% CI 0.49 to 2.18; 7 RCTs, 6384 participants, moderate-certainty evidence). There was one reported case in which raised ALT occurred with raised bilirubin. No study reported severe drug-induced liver injury. Electrocardiograph (ECG) abnormalities were less common with pyronaridine-artesunate compared to other antimalarials. We identified no other safety concerns. NRS safety review A review on safety in NRS allowed us to increase the population within which safety was assessed. We included seven studies with 9546 participants: five single-arm observational studies, one cohort event monitoring study, and one dose-escalation study. All studies provided data on adverse event frequency, with a small number of participants experiencing serious adverse events and adverse effects related to pyronaridine: serious adverse events average 0.37%; drug-related 9.0%. In two studies reporting elevations in liver enzymes, small percentages of participants (2.4% and 14.1% respectively) experienced increases in either ALT, AST, or bilirubin on day 7; however, these were small increases that returned to normal by day 42. AUTHORS' CONCLUSIONS: Pyronaridine-artesunate was efficacious against uncomplicated P falciparum malaria; achieved a PCR-adjusted treatment failure rate of less than 5% at days 28 and 42; and may be at least as good as, or better than, other marketed ACTs. Pyronaridine-artesunate increases the risk of episodes of abnormally raised ALT. The observational data did not signal an excess of clinically important adverse effects.

Malnutrition

(Papers in past years listed in this section refer to the management of protein-energy malnutrition. For other relevant studies of nutrition see also Nutrition, Vitamin A, Vitamin D, Maternal health, Anaemia and iron deficiency)

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Predictors of recovery in children aged 6-59 months with uncomplicated severe acute malnutrition: a multicentre study

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Abstract

Objective: To identify predictors of recovery in children with uncomplicated severe acute malnutrition (SAM).

Design: This is a secondary data analysis from an individual randomised controlled trial, where children with uncomplicated SAM were randomised to three feeding regimens, namely ready-to-use therapeutic food (RUTF) sourced from Compact India, locally prepared RUTF or augmented home-prepared foods, under two age strata (6-17 months and 18-59

months) for 16 weeks or until recovery. Three sets of predictors that could influence recovery, namely child, family and nutritional predictors, were analysed.
Setting: Rural and urban slum areas of three states of India, namely Rajasthan, Delhi and Tamil Nadu.
Participants: In total, 906 children (age: 6-59 months) were analysed to estimate the adjusted hazard ratio (AHR) using the Cox proportional hazard ratio model to identify various predictors.
Results: Being a female child (AHR: 1·269 (1·016, 1·584)), better employment status of the child's father (AHR: 1·53 (1·197, 1·95)) and residence in a rental house (AHR: 1·485 (1·137, 1·94)) increased the chances of recovery. No hospitalisation (AHR: 1·778 (1·055, 2·997)), no fever, (AHR: 2·748 (2·161, 3·494)) and ≤ 2 episodes of diarrhoea (AHR: 1·579 (1·035, 2·412)) during the treatment phase; availability of community-based peer support to mothers for feeding (AHR: 1·61 (1·237, 2·097)) and a better weight-for-height Z-score (WHZ) at enrolment (AHR: 1·811 (1·297, 2·529)) predicted higher chances of recovery from SAM.
Conclusion: The probability of recovery increases in children with better WHZ and with the initiation of treatment for acute illnesses to avoid hospitalisation, availability of peer support and better employment status of the father.

Maternal health

(see also Malaria)

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doi: 10.1016/j.eclinm.2022.101309. eCollection 2022 Mar.
Characteristics and birth outcomes of pregnant adolescents compared to older women: An analysis of individual level data from 140,000 mothers from 20 RCTs
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Abstract
Background: Adolescence is a critical period of maturation when nutrient needs are high, especially among adolescents entering pregnancy. Using individual-level data from 140,000 participants, we examined socioeconomic, nutrition, and pregnancy and birth outcomes for adolescent mothers (10-19 years) compared to older mothers in low and middle-income countries.
Methods: This study was conducted between March 16, 2018 and May 25, 2021. Data were obtained from 20 randomised controlled trials of micronutrient supplementation in pregnancy. Stratified analyses were conducted by age (10-14 years, 15-17 years, 18-19 years, 20-29 years, 30-39 years, 40+ years) and geographical region (Africa, Asia). Crude and confounder-adjusted means, prevalence and relative risks of pregnancy, nutrition and birth

outcomes were estimated using multivariable linear and log-binomial regression models with 95% confidence intervals.
Findings: Adolescent mothers comprised 31.6% of our data. Preterm birth, small-for-gestational age (SGA), low birthweight (LBW) and newborn mortality followed a U-shaped trend in which prevalence was highest among the youngest mothers (10-14 years) and then reduced gradually, but increased again for older mothers (40+ years). When compared to mothers aged 20-29 years, there was a 23% increased risk of preterm birth, a 60% increased risk of perinatal mortality, a 63% increased risk of neonatal mortality, a 28% increased risk of LBW, and a 22% increased risk of SGA among mothers 10-14 years. Mothers 40+ years experienced a 22% increased risk of preterm birth and a 103% increased risk of stillbirth when compared to the 20-29 year group.
Interpretation: The youngest and oldest mothers suffer most from adverse pregnancy and birth outcomes. Policy and programming agendas should consider both biological and socioeconomic/environmental factors when targeting these populations.

Antenatal care

Matern Child Health J. 2022 Apr 6.
doi: 10.1007/s10995-022-03409-2. Online ahead of print.
Can Flip-Chart Assisted Maternal Education Improve Essential New Born Care Knowledge and Skills? A Randomized Controlled Trial
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Abstract
Background: Despite the implementation of essential newborn care (ENC) by the World Health Organization, knowledge gaps among postpartum women persist. Inappropriate breastfeeding practices and lack of knowledge regarding ENC among mothers has resulted in higher neonatal mortality.
Purpose: Our study focused on evaluating the effectiveness of flip-chart assisted postpartum maternal education in improving ENC knowledge and skills.
Material and methods: A single blind parallel randomized controlled trial was carried out with 120 primigravidae. Participants were allocated to the intervention group (IG) or the control group (CG) by block randomization. A pretested validated questionnaire was administered to participants in both groups within 24 h post-delivery. Women in the IG were provided flip-chart assisted education regarding ENC approximately 24 h post-delivery. Women in both groups received verbal advice on ENC from the postnatal ward nurses, as per the existing hospital policy. ENC skills were observed in all participants in postnatal wards by independent observers. 6 months later, knowledge retention was assessed and analyzed in both groups.
Results: Antenatal education remained at 32% among all postnatal women. Postnatal flip-chart-assisted maternal education had a significant impact on ENC skills in the IG ($p < 0.01$) and precipitated higher knowledge scores at the end of 6 months ($p < 0.01$) in the IG.
Conclusion for practice: Flip-chart assisted education soon after delivery had a sustained effect on ENC knowledge and practices that persisted for 6 months post-delivery.

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A systematic review and narrative synthesis of antenatal interventions to improve maternal and neonatal health in Nepal

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Abstract

Background: Maternal and neonatal mortality rates remain high in many economically underdeveloped countries, including Nepal, and good quality antenatal care can reduce adverse pregnancy outcomes. However, identifying how to best improve antenatal care can be challenging.

Objective: To identify the interventions that have been investigated in the antenatal period in Nepal for maternal or neonatal benefit. We wanted to understand their scale, location, cost, and effectiveness.

Study design: Online bibliographic databases (Cochrane Central, MEDLINE, Embase, CINAHL Plus, British Nursing Index, PsycInfo, Allied and Complementary Medicine) and trial registries (ClinicalTrials.gov and the World Health Organization Clinical Trials Registry Platform) were searched from their inception till May 24, 2020. We included all studies reporting any maternal or neonatal outcome after an intervention in the antenatal period. We screened the studies and extracted the data in duplicate. A meta-analysis was not possible because of the heterogeneity of the interventions and outcomes, so we performed a narrative synthesis of the included studies.

Results: A total of 25 studies met our inclusion criteria. These studies showed a variety of approaches toward improving antenatal care (eg, educational programs, incentive schemes, micronutrient supplementation) in different settings (home, community, or hospital-based) and with a wide variety of outcomes. Less than a quarter of the studies were randomized controlled trials, and many were single-site or reported only short-term outcomes. All studies reported having made a positive impact on antenatal care in some way, but only 3 provided a cost-benefit analysis to support implementation. None of these studies focused on the most remote communities in Nepal.

Conclusion: Our systematic review found good quality evidence that micronutrient supplementation and educational interventions can bring important clinical benefits. Iron and folic acid supplementation significantly reduces neonatal mortality and maternal anemia, whereas birth preparedness classes increase the uptake of antenatal and postnatal care, compliance with micronutrient supplementation, and awareness of the danger signs in pregnancy.

Maternal malaria prevention

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A cluster randomized trial of delivery of intermittent preventive treatment of malaria in pregnancy at the community level in Malawi

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DOI: 10.1186/s12936-022-04216-4
Abstract
Background: Malaria in pregnancy doubles the risk of low birthweight; up to 11% of all neonatal deaths in sub-Saharan Africa are associated with malaria in pregnancy. To prevent these and other adverse health consequences, the World Health Organization recommends administering intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine for all pregnant women at each antenatal care (ANC) visit, starting as early as possible in the second trimester. The target is for countries to administer a minimum of three doses (IPTp3+) to at least 85% of pregnant women.
Methods: A cluster randomized, controlled trial was conducted to assess the effect of delivery of IPTp by community health workers on the coverage of IPTp3 + and ANC visits in Malawi. Community delivery of IPTp was implemented within two districts in Malawi over a 21-month period, from November 2018 to July 2020. In control sites, IPTp was delivered at health facilities. Representative samples of women who delivered in the prior 12 months were surveyed at baseline (n = 370, December 2017) and endline (n = 687, August 2020). A difference in differences analysis was conducted to assess the change in coverage of IPTp and ANC over time, accounting for clustering at the health facility level.
Results: Overall IPTp coverage increased over the study period. At baseline, women received a mean of 2.3 IPTp doses (range 0-5 doses) across both arms, and at endline, women received a mean of 2.8 doses (range 0-9 doses). Despite overall increases, the change in IPTp3 + coverage was not significantly different between intervention and control groups (6.9%, 95% CI: -5.9%, 19.6%). ANC4 + coverage increased significantly in the intervention group compared with the control group, with a difference-in-differences of 25.3% points (95% CI: 1.3%, 49.3%).
Conclusions: In order to reduce the burden of malaria in pregnancy, new strategies are needed to improve uptake of effective interventions such as IPTp. While community health workers' delivery of IPTp did not increase uptake in this study, they may be effective in other settings or circumstances. Further research can help identify the health systems characteristics that are conducive to community delivery of IPTp and the operational requirements for effective implementation.

Obstetric care and delivery

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doi: 10.1186/s12913-022-07650-x.
Implementing the WHO Safe Childbirth Checklist modified for preterm birth: lessons learned and experiences from Kenya and Uganda
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Abstract

Background: The WHO Safe Childbirth Checklist (SCC) contains 29 evidence-based practices (EBPs) across four pause points spanning admission to discharge. It has been shown to increase EBP uptake and has been tailored to specific contexts. However, little research has been conducted in East Africa on use of the SCC to improve intrapartum care, particularly for preterm birth despite its burden. We describe checklist adaptation, user acceptability, implementation and lessons learned.
Methods: The East Africa Preterm Birth Initiative (PTBi EA) modified the SCC for use in 23 facilities in Western Kenya and Eastern Uganda as part of a cluster randomized controlled trial evaluating a package of facility-based interventions to improve preterm birth outcomes. The modified SCC (mSCC) for prematurity included: addition of a triage pause point before admission; focus on gestational age assessment, identification and management of preterm labour; and alignment with national guidelines. Following introduction, implementation lasted 24 and 34 months in Uganda and Kenya respectively and was supported through complementary mentoring and data strengthening at all sites. PRONTO® simulation training and quality improvement (QI) activities further supported mSCC use at intervention facilities only. A mixed methods approach, including checklist monitoring, provider surveys and in-depth interviews, was used in this analysis.
Results: A total of 19,443 and 2229 checklists were assessed in Kenya and Uganda, respectively. In both countries, triage and admission pause points had the highest rates of completion. Kenya's completion was greater than 70% for all pause points; Uganda ranged from 39 to 75%. Intervention facilities exposed to PRONTO and QI had higher completion rates than control sites. Provider perceptions cited clinical utility of the checklist, particularly when integrated into patient charts. However, some felt it repeated information in other documentation tools. Completion was hindered by workload and staffing issues.
Conclusion: This study highlights the feasibility and importance of adaptation, iterative modification and complementary activities to reinforce SCC use. There are important opportunities to improve its clinical utility by the addition of prompts specific to the needs of different contexts. The trial assessing the PTBi EA intervention package was registered at ClinicalTrials.gov NCT03112018 Registered December 2016, retrospectively registered.

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Low-dose oral misoprostol for induction of labour

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Abstract
Background: Misoprostol given orally is a commonly used labour induction method. Our Cochrane Review is restricted to studies with low-dose misoprostol (initially ≤ 50 µg), as higher doses pose unacceptably high risks of uterine hyperstimulation.
Objectives: To assess the efficacy and safety of low-dose oral misoprostol for labour induction in women with a viable fetus in the third trimester of pregnancy.
Search methods: We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (14 February 2021) and reference lists of retrieved studies.
Selection criteria: Randomised trials comparing low-dose oral misoprostol (initial dose ≤ 50 µg) versus placebo, vaginal dinoprostone, vaginal misoprostol, oxytocin, or mechanical

methods; or comparing oral misoprostol protocols (one- to two-hourly versus four- to six-hourly; 20 µg to 25 µg versus 50 µg; or 20 µg hourly titrated versus 25 µg two-hourly static).
Data collection and analysis: Using Covidence, two review authors independently screened reports, extracted trial data, and performed quality assessments. Our primary outcomes were vaginal birth within 24 hours, caesarean section, and hyperstimulation with foetal heart changes.
Main results: We included 61 trials involving 20,026 women. GRADE assessments ranged from moderate- to very low-certainty evidence, with downgrading decisions based on imprecision, inconsistency, and study limitations. Oral misoprostol versus placebo/no treatment (four trials; 594 women) Oral misoprostol may make little to no difference in the rate of caesarean section (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.59 to 1.11; 4 trials; 594 women; moderate-certainty evidence), while its effect on uterine hyperstimulation with foetal heart rate changes is uncertain (RR 5.15, 95% CI 0.25 to 105.31; 3 trials; 495 women; very low-certainty evidence). Vaginal births within 24 hours was not reported. In all trials, oxytocin could be commenced after 12 to 24 hours and all women had pre-labour ruptured membranes. Oral misoprostol versus vaginal dinoprostone (13 trials; 9676 women) Oral misoprostol probably results in fewer caesarean sections (RR 0.84, 95% CI 0.78 to 0.90; 13 trials, 9676 women; moderate-certainty evidence). Subgroup analysis indicated that 10 µg to 25 µg (RR 0.80, 95% CI 0.74 to 0.87; 9 trials; 8652 women) may differ from 50 µg (RR 1.10, 95% CI 0.91 to 1.34; 4 trials; 1024 women) for caesarean section. Oral misoprostol may decrease vaginal births within 24 hours (RR 0.93, 95% CI 0.87 to 1.00; 10 trials; 8983 women; low-certainty evidence) and hyperstimulation with foetal heart rate changes (RR 0.49, 95% CI 0.40 to 0.59; 11 trials; 9084 women; low-certainty evidence). Oral misoprostol versus vaginal misoprostol (33 trials; 6110 women) Oral use may result in fewer vaginal births within 24 hours (average RR 0.81, 95% CI 0.68 to 0.95; 16 trials, 3451 women; low-certainty evidence), and less hyperstimulation with foetal heart rate changes (RR 0.69, 95% CI 0.53 to 0.92, 25 trials, 4857 women, low-certainty evidence), with subgroup analysis suggesting that 10 µg to 25 µg orally (RR 0.28, 95% CI 0.14 to 0.57; 6 trials, 957 women) may be superior to 50 µg orally (RR 0.82, 95% CI 0.61 to 1.11; 19 trials; 3900 women). Oral misoprostol probably does not increase caesarean sections overall (average RR 1.00, 95% CI 0.86 to 1.16; 32 trials; 5914 women; low-certainty evidence) but likely results in fewer caesareans for foetal distress (RR 0.74, 95% CI 0.55 to 0.99; 24 trials, 4775 women). Oral misoprostol versus intravenous oxytocin (6 trials; 737 women, 200 with ruptured membranes) Misoprostol may make little or no difference to vaginal births within 24 hours (RR 1.12, 95% CI 0.95 to 1.33; 3 trials; 466 women; low-certainty evidence), but probably results in fewer caesarean sections (RR 0.67, 95% CI 0.50 to 0.90; 6 trials; 737 women; moderate-certainty evidence). The effect on hyperstimulation with foetal heart rate changes is uncertain (RR 0.66, 95% CI 0.19 to 2.26; 3 trials, 331 women; very low-certainty evidence). Oral misoprostol versus mechanical methods (6 trials; 2993 women) Six trials compared oral misoprostol to transcervical Foley catheter. Misoprostol may increase vaginal birth within 24 hours (RR 1.32, 95% CI 0.98 to 1.79; 4 trials; 1044 women; low-certainty evidence), and probably reduces the risk of caesarean section (RR 0.84, 95% CI 0.75 to 0.95; 6 trials; 2993 women; moderate-certainty evidence). There may be little or no difference in hyperstimulation with foetal heart rate changes (RR 1.31, 95% CI 0.78 to 2.21; 4 trials; 2828 women; low-certainty evidence). Oral misoprostol one- to two-hourly versus four- to six-hourly (1 trial; 64 women) The evidence on hourly titration was very uncertain due to the low numbers reported. Oral misoprostol 20 µg hourly titrated versus 25 µg two-hourly static (2 trials; 296 women) The difference in regimen

may have little or no effect on the rate of vaginal births in 24 hours (RR 0.97, 95% CI 0.80 to 1.16; low-certainty evidence). The evidence is of very low certainty for all other reported outcomes.
Authors' conclusions: Low-dose oral misoprostol is probably associated with fewer caesarean sections (and therefore more vaginal births) than vaginal dinoprostone, and lower rates of hyperstimulation with foetal heart rate changes. However, time to birth may be increased, as seen by a reduced number of vaginal births within 24 hours. Compared to transcervical Foley catheter, low-dose oral misoprostol is associated with fewer caesarean sections, but equivalent rates of hyperstimulation. Low-dose misoprostol given orally rather than vaginally is probably associated with similar rates of vaginal birth, although rates may be lower within the first 24 hours. However, there is likely less hyperstimulation with foetal heart changes, and fewer caesarean sections performed due to foetal distress. The best available evidence suggests that low-dose oral misoprostol probably has many benefits over other methods for labour induction. This review supports the use of low-dose oral misoprostol for induction of labour, and demonstrates the lower risks of hyperstimulation than when misoprostol is given vaginally. More trials are needed to establish the optimum oral misoprostol regimen, but these findings suggest that a starting dose of 25 µg may offer a good balance of efficacy and safety.

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doi: 10.1002/ijgo.13963. Epub 2021 Oct 26.
"Suction Tube Uterine Tamponade" for treatment of refractory postpartum hemorrhage: Internal feasibility and acceptability pilot of a randomized clinical trial
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DOI: 10.1002/ijgo.13963
Abstract
Objective: To assess feasibility and acceptability of a novel, low-cost "Suction Tube Uterine Tamponade" (STUT) treatment for refractory postpartum hemorrhage (PPH).
Methods: We allocated patients with refractory PPH by randomly ordered envelopes to STUT or routine uterine balloon tamponade (UBT, Ellavi free-flow system) in 10 hospitals in South Africa. In the STUT group, a 24FG Levin stomach tube was inserted into the uterine cavity and vacuum created with a vacuum pump or manual vacuum aspiration syringe.
Results: For this internal pilot study, 12 participants were allocated to STUT and 12 to UBT. Insertion failed in one of each group and was recorded as difficult in 3/10 STUT and 4/9 UBT insertions respectively (five missing data). There were two laparotomies and one intensive care unit admission in the UBT group. Pain during STUT insertion was graded as none/mild in 9/10 and severe in 1/10. The experience of the STUT procedure was graded as fine in 4/11 and "uncomfortable but acceptable" in 7/11.
Conclusion: STUT is feasible and acceptable, justifying continuation of our trial. These data will also inform a large World Health Organization trial to test effectiveness of uterine tamponade methods. The numbers are too small to support any clinical recommendation.

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Effectiveness of uterine tamponade devices for refractory postpartum haemorrhage after vaginal birth: a systematic review

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Abstract

Objectives: To evaluate uterine tamponade devices' effectiveness for atonic refractory postpartum haemorrhage (PPH) after vaginal birth and the effect of including them in institutional protocols.

Search strategy: PubMed, EMBASE, CINAHL, LILACS, POPLINE, from inception to January 2021.

Study selection: Randomised and non-randomised comparative studies.

Outcomes: Composite outcome including surgical interventions (artery ligations, compressive sutures or hysterectomy) or maternal death, and hysterectomy.

Results: All included studies were at high risk of bias. The certainty of the evidence was rated as very low to low. One randomised study measured the effect of the condom-catheter balloon compared with standard care and found unclear results for the composite outcome (relative risk [RR] 2.33, 95% CI 0.76-7.14) and hysterectomy (RR 4.14, 95% CI 0.48-35.93). Three comparative studies assessed the effect of including uterine balloon tamponade in institutional protocols. A stepped wedge cluster randomised controlled trial suggested an increase in the composite outcome (RR 4.08, 95% CI 1.07-15.58) and unclear results for hysterectomy (RR 4.38, 95% CI 0.47-41.09) with the use of the condom-catheter or surgical glove balloon. One non-randomised study showed unclear effects on the composite outcome (RR 0.33, 95% CI 0.11-1.03) and hysterectomy (RR 0.49, 95% CI 0.04-5.38) after the inclusion of the Bakri balloon. The second non-randomised study found unclear effects on the composite outcome (RR 0.95, 95% CI 0.32-2.81) and hysterectomy (RR 1.84, 95% CI 0.44-7.69) after the inclusion of Ebb or Bakri balloon.

Conclusions: The effect of uterine tamponade devices for the management of atonic refractory PPH after vaginal delivery is unclear, as is the role of the type of device and the setting.

Reprod Health. 2021 Jun 2;18(1):110.
doi: 10.1186/s12978-021-01159-y.

Planned early delivery for late preterm pre-eclampsia in a low- and middle-income setting: a feasibility study

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Abstract

Background: Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity globally. Planned delivery between 34^{+0} and 36^{+6} weeks may reduce adverse

pregnancy outcomes but is yet to be evaluated in a low and middle-income setting. Prior to designing a randomised controlled trial to evaluate this in India and Zambia, we carried out a 6-month feasibility study in order to better understand the proposed trial environment and guide development of our intervention.
Methods: We used mixed methods to understand the disease burden and current management of pre-eclampsia at our proposed trial sites and explore the acceptability of the intervention. We undertook a case notes review of women with pre-eclampsia who delivered at the proposed trial sites over a 3-month period, alongside facilitating focus group discussions with women and partners and conducting semi-structured interviews with healthcare providers. Descriptive statistics were used to analyse audit data. A thematic framework analysis was used for qualitative data.
Results: Case notes data (n = 326) showed that in our settings, 19.5% (n = 44) of women with pre-eclampsia delivering beyond 34 weeks experienced an adverse outcome. In women delivering between 34^{+0} and 36^{+6} weeks, there were similar numbers of antenatal stillbirths [n = 3 (3.3%)] and neonatal deaths [n = 3 (3.4%)]; median infant birthweight was 2.2 kg and 1.9 kg in Zambia and India respectively. Lived experience of women and healthcare providers was an important facilitator to the proposed intervention, highlighting the serious consequences of pre-eclampsia. A preference for spontaneous labour and limited neonatal resources were identified as potential barriers.
Conclusions: This study demonstrated a clear need to evaluate the intervention and highlighted several challenges relating to trial context that enabled us to adapt our protocol and design an acceptable intervention. Our study demonstrates the importance of assessing feasibility when developing complex interventions, particularly in a low-resource setting. Additionally, it provides a unique insight into the management of pre-eclampsia at our trial settings and an understanding of the knowledge, attitudes and beliefs underpinning the acceptability of planned early delivery.

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Intrapartum care algorithms for liquor abnormalities: oligohydramnios, meconium, blood and purulent discharge

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Abstract
Aim: To construct evidence-based algorithms for the assessment and management of common amniotic fluid abnormalities detected during labour.
Population: Low-risk singleton, term pregnant women in labour.
Setting: Birth facilities in low- and middle-income countries.
Search strategy: We searched international guidelines published by the American College of Obstetricians and Gynecologists (ACOG), the National Institute for Health and Care Excellence (NICE), the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), the Royal College of Obstetricians and Gynaecologists (RCOG), the Society of Obstetrics and Gynaecology (SOGC) and the World Health Organization (WHO). We also searched The Cochrane Library and MEDLINE up to 20 January 2020 using keywords for relevant systematic reviews and randomised trials.

Case scenarios: We developed evidence-based intrapartum care algorithms for four case scenarios: oligohydramnios; meconium-stained amniotic fluid; bloody amniotic fluid or vaginal bleeding; and purulent amniotic fluid or discharge. These conditions may be associated with fetal and /or maternal morbidity. Differential diagnosis includes uteroplacental insufficiency, fetal growth restriction, fetal distress, abruption, placenta or vasa praevia, uterine rupture and intra-amniotic infection, respectively. Algorithms include how to assess for, diagnose and manage these conditions.
Conclusions: Four algorithms are presented, to provide a systematic approach and guidance on the clinical management for the following amniotic fluid abnormalities: oligohydramnios; meconium-stained liquor; bloody amniotic fluid or vaginal bleeding; and purulent amniotic fluid or discharge. These algorithms may be beneficial in supporting clinical decision making, particularly in low-resource settings.

JAMA Netw Open. 2021 Dec 1;4(12):e2137168.
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Effects of the World Health Organization Safe Childbirth Checklist on Quality of Care and Birth Outcomes in Aceh, Indonesia: A Cluster-Randomized Clinical Trial

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Abstract

Importance: To address major causes of perinatal and maternal mortality, the World Health Organization developed the Safe Childbirth Checklist (SCC), which to our knowledge has been rigorously evaluated only in combination with high-intensity coaching.
Objective: To evaluate the effect of the SCC with medium-intensity coaching on health care workers' performance of essential birth practices.
Design, setting, and participants: This cluster randomized clinical trial without blinding included 32 hospitals and community health centers in the province of Aceh, Indonesia (a medium-resource setting) that met the criterion of providing at least basic emergency obstetric and newborn care. Baseline data were collected from August to October 2016, and outcomes were measured from March to April 2017. Data were analyzed from January 2020 to October 2021.
Interventions: After applying an optimization method, facilities were randomly assigned to the treatment or control group (16 facilities each). The SCC with 11 coaching visits was implemented during a 6-month period.
Main outcomes and measures: For the primary outcome, clinical observers documented whether 36 essential birth practices were applied at treatment and control facilities at 1 or more of 4 pause points during the birthing process (admission to the hospital, just before pushing or cesarean delivery, soon after birth, and before hospital discharge). Probability models for binary outcome measures were estimated using ordinary least-squares regressions, complemented by Firth logit and complier average causal effect estimations.
Results: Among the 32 facilities that participated in the trial, a significant increase of up to 41 percentage points was observed in the application of 5 of 36 essential birth practices in the 16 treatment facilities compared with the 16 control facilities, including communication of danger signs at admission (treatment: 136 of 155 births [88%]; control: 79 of 107 births

[74%]), measurement of neonatal temperature (treatment: 9 of 31 births [29%]; control: 1 of 20 births [5%]), newborn feeding checks (treatment: 22 of 34 births [65%]; control: 5 of 21 births [24%]), and the rate of communication of danger signs to mothers and birth companions verbally (treatment: 30 of 36 births [83%]; control: 14 of 22 births [64%]) and in a written format (treatment: 3 of 24 births [13%]; control: 0 of 16 births [0%]).
Conclusions and relevance: In this cluster randomized clinical trial, health facilities that implemented the SCC with medium-intensity coaching had an increased rate of application for 5 of 36 essential birth practices compared with the control facilities. Medium-intensity coaching may not be sufficient to increase uptake of the SCC to a satisfying extent, but it may be worthwhile to assess a redesigned coaching approach prompting long-term behavioral change and, therefore, effectiveness.

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The effect of Zhang's guideline vs the WHO partograph on childbirth experience measured by the Childbirth Experience Questionnaire in the Labor Progression Study (LaPS): A cluster randomized trial

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Abstract
Introduction: Childbirth experience is an increasingly recognized and important measure of quality of obstetric care. Previous research has shown that it can be affected by intrapartum care and how labor is followed. A partograph is recommended to follow labor progression by recording cervical dilation over time. There are currently different guidelines in use worldwide to follow labor progression. The two main ones are the partograph recommended by the World Health Organization (WHO) based on the work of Friedman and Philpott and a guideline based on Zhang's research. In our study we assessed the effect of adhering to Zhang's guideline or the WHO partograph on childbirth experience. Zhang's guideline describes expected normal labor progression based on data from contemporary obstetric populations, resulting in an exponential progression curve, compared with the linear WHO partograph. The choice of labor curve affects the intrapartum follow-up of women and this could potentially affect childbirth experience.
Material and methods: The Labor Progression Study (LaPS) study was a prospective, cluster randomized controlled trial conducted at 14 birth centers in Norway. Birth centers were randomized to either follow Zhang's guideline or the WHO partograph. Nulliparous women in active labor, with one fetus in cephalic presentation at term and spontaneous labor onset were included. At 4 weeks postpartum, included women received an online login to complete the Childbirth Experience Questionnaire (CEQ). Total score on the CEQ, the four domain scores on the CEQ, and scores on the individual items on the CEQ were compared between the two groups.
Results: There were 1855 women in the Zhang group and 1749 women in the WHO partograph group. There was no difference in the total or domain CEQ scores between the two groups. We found statistically significant differences for two individual items; women in the Zhang group scored lower on positive memories and feeling of control.

J Matern Fetal Neonatal Med. 2021 Nov 11;1-8.
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Effect of heat stable carbetocin vs oxytocin for preventing postpartum haemorrhage on post delivery hemoglobin-a randomized controlled trial

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Abstract

Objective: To compare the effect of heat-stable carbetocin 100 µg IM versus oxytocin 10 IU IM on post-delivery hemoglobin level.

Setting: Hospital based study in Southern India.

Population: Women delivering vaginally who were enrolled in the WHO CHAMPION trial in a single facility in India. WHO CHAMPION Trial was a randomized, double-blind, noninferiority trial comparing intramuscular injections of heat-stable carbetocin with oxytocin administered immediately after vaginal birth in women across 23 sites in 10 countries.

Methods: This was a nested randomized controlled trial designed to compare the effect of heat-stable carbetocin 100 µg IM versus oxytocin 10 IU IM, administered within one minute of vaginal delivery of the baby for prevention of postpartum hemorrhage, on post-delivery 48-72 h hemoglobin level, adjusted for pre-delivery hemoglobin level. 1,799 women from one hospital in India participated in this study.

Results: Pre-delivery hemoglobin and postpartum blood loss were not significantly different between carbetocin and oxytocin. Post-delivery hemoglobin, unadjusted or adjusted for pre-delivery hemoglobin, was slightly lower for carbetocin (10.09 g/dL) compared to oxytocin (10.21) (p value of 0.0432). The drop in hemoglobin was slightly higher for carbetocin, although the difference was very small (1.2 g/dL for carbetocin, 1.1 g/dL for oxytocin) (*p* value of .0786). The proportion of participants with a drop in hemoglobin of 2 g/dL or more, adjusted for pre-delivery hemoglobin, was higher for carbetocin (RR = 1.29, 95% CI 1.02-1.63). From the regression coefficients it can be derived that post-delivery hemoglobin, adjusted for pre-delivery hemoglobin, decreases on average 0.12 g/dL for each dL of blood lost, for the two treatments combined.

Conclusion: The present ancillary study showed that intramuscular administration of 100 µg of heat stable carbetocin can result in a slightly lower post-delivery hemoglobin, slightly higher drop and higher percentage of women having a drop of 2 g/dL or larger, compared to 10 IU of oxytocin.

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Modification of oxytocin use through a coaching-based intervention based on the WHO Safe Childbirth Checklist in Uttar Pradesh, India: a secondary analysis of a cluster randomised controlled trial

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Abstract

Objective: To understand the prevalence of intrapartum oxytocin use, assess associated perinatal and maternal outcomes, and evaluate the impact of a WHO Safe Childbirth Checklist intervention on oxytocin use at primary-level facilities in Uttar Pradesh, India.
Design: Secondary analysis of a cluster-randomised controlled trial.
Setting: Thirty Primary and Community public health facilities in Uttar Pradesh, India from 2014 to 2017.
Population: Women admitted to a study facility for childbirth at baseline, 2, 6 or 12 months after intervention initiation.
Methods: The BetterBirth intervention aimed to increase adherence to the WHO Safe Childbirth Checklist. We used Rao-Scott Chi-square tests to compare (1) timing of oxytocin use between study arms and (2) perinatal mortality and resuscitation of infants whose mothers received intrapartum oxytocin versus who did not.
Main outcome measures: Intrapartum and postpartum oxytocin administration, perinatal mortality, use of neonatal bag and mask.
Results: We observed 5484 deliveries. At baseline, intrapartum oxytocin was administered to 78.2% of women. Two months after intervention initiation, intrapartum oxytocin (I) was administered to 32.1% of women compared with 70.6% in the control (C) ($P < 0.01$); this difference diminished after the end of the intervention (I = 48.2%, C = 74.7%, P = 0.03). Partograph use remained at <1% at all facilities. Resuscitation was performed on 7.5% of infants whose mother received intrapartum oxytocin versus 2.0% who did not ($P < 0.0001$).
Conclusions: In this setting, intrapartum oxytocin use was high despite limited maternal/fetal monitoring or caesarean capability, and was associated with increased neonatal resuscitation. The BetterBirth intervention was successful at decreasing intrapartum oxytocin use. Ongoing support is needed to sustain these practices.

Maternal nutrition and micronutrient supplementation

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Calcium supplementation during pregnancy and long-term offspring outcome: a systematic literature review and meta-analysis

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Abstract
The World Health Organization currently recommends calcium supplementation for pregnant women, especially those with low calcium intakes, to reduce the risk of hypertension and preeclampsia. We aimed to evaluate the effect of this intervention on selected offspring outcomes. A systematic search was conducted in 11 databases for published randomized controlled trials (RCTs) on the effect of maternal calcium supplementation with or without vitamin D during pregnancy on selected offspring cardiovascular, growth, and metabolic and neurodevelopmental outcomes. Screening of titles and abstracts of 3555 records and full texts of 31 records yielded six RCTs (nine reports, n = 1616). Forest plot analyses were performed if at least two studies presented comparable data on the same outcome. In one study (n = 591), high-dose calcium supplementation

during pregnancy was associated with a decreased risk of offspring high systolic blood pressure at 5-7 years of age (risk ratio = 0.59; 95% confidence interval: 0.39-0.90). The effects of the intervention on offspring growth, metabolic, and neurodevelopmental outcomes remain unknown because of conflicting or insufficient data. High risk of attrition bias decreased the quality of the evidence. Limited available data from RCTs do not provide sufficient evidence to conclude that prenatal calcium supplementation influences offspring health outcomes beyond the newborn period.

Post-natal maternal care

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doi: 10.1002/14651858.CD009326.pub4.

Schedules for home visits in the early postpartum period

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Abstract

Background: Maternal complications, including psychological/mental health problems and neonatal morbidity, have commonly been observed in the postpartum period. Home visits by health professionals or lay supporters in the weeks following birth may prevent health problems from becoming chronic, with long-term effects. This is an update of a review last published in 2017.

Objectives: The primary objective of this review is to assess the effects of different home-visiting schedules on maternal and newborn mortality during the early postpartum period. The review focuses on the frequency of home visits (how many home visits in total), the timing (when visits started, e.g. within 48 hours of the birth), duration (when visits ended), intensity (how many visits per week), and different types of home-visiting interventions.

Search methods: For this update, we searched the Cochrane Pregnancy and Childbirth Group's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (19 May 2021), and checked reference lists of retrieved studies.

Selection criteria: Randomised controlled trials (RCTs) (including cluster-, quasi-RCTs and studies available only as abstracts) comparing different home-visiting interventions that enrolled participants in the early postpartum period (up to 42 days after birth) were eligible for inclusion. We excluded studies in which women were enrolled and received an intervention during the antenatal period (even if the intervention continued into the postnatal period), and studies recruiting only women from specific high-risk groups (e.g. women with alcohol or drug problems).

Data collection and analysis: Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We used the GRADE approach to assess the certainty of the evidence.

Main results: We included 16 randomised trials with data for 12,080 women. The trials were carried out in countries across the world, in both high- and low-resource settings. In low-resource settings, women receiving usual care may have received no additional postnatal care after early hospital discharge. The interventions and controls varied considerably across studies. Trials focused on three broad types of comparisons, as detailed below. In all but four of the included studies, postnatal care at home was delivered by healthcare professionals. The aim of all interventions was broadly to assess the well-being of mothers and babies, and

to provide education and support. However, some interventions had more specific aims, such as to encourage breastfeeding, or to provide practical support. For most of our outcomes, only one or two studies provided data, and results were inconsistent overall. All studies had several domains with high or unclear risk of bias. More versus fewer home visits (five studies, 2102 women) The evidence is very uncertain about whether home visits have any effect on maternal and neonatal mortality (very low-certainty evidence). Mean postnatal depression scores as measured with the Edinburgh Postnatal Depression Scale (EPDS) may be slightly higher (worse) with more home visits, though the difference in scores was not clinically meaningful (mean difference (MD) 1.02, 95% confidence interval (CI) 0.25 to 1.79; two studies, 767 women; low-certainty evidence). Two separate analyses indicated conflicting results for maternal satisfaction (both low-certainty evidence); one indicated that there may be benefit with fewer visits, though the 95% CI just crossed the line of no effect (risk ratio (RR) 0.96, 95% CI 0.90 to 1.02; two studies, 862 women). However, in another study, the additional support provided by health visitors was associated with increased mean satisfaction scores (MD 14.70, 95% CI 8.43 to 20.97; one study, 280 women; low-certainty evidence). Infant healthcare utilisation may be decreased with more home visits (RR 0.48, 95% CI 0.36 to 0.64; four studies, 1365 infants) and exclusive breastfeeding at six weeks may be increased (RR 1.17, 95% CI 1.01 to 1.36; three studies, 960 women; low-certainty evidence). Serious neonatal morbidity up to six months was not reported in any trial. Different models of postnatal care (three studies, 4394 women) In a cluster-RCT comparing usual care with individualised care by midwives, extended up to three months after the birth, there may be little or no difference in neonatal mortality (RR 0.97, 95% CI 0.85 to 1.12; one study, 696 infants). The proportion of women with EPDS scores ≥ 13 at four months is probably reduced with individualised care (RR 0.68, 95% CI 0.53 to 0.86; one study, 1295 women). One study suggests there may be little to no difference between home visits and telephone screening in neonatal morbidity up to 28 days (RR 0.97, 95% CI 0.85 to 1.12; one study, 696 women). In a different study, there was no difference between breastfeeding promotion and routine visits in exclusive breastfeeding rates at six months (RR 1.47, 95% CI 0.81 to 2.69; one study, 656 women). Home versus facility-based postnatal care (eight studies, 5179 women) The evidence suggests there may be little to no difference in postnatal depression rates at 42 days postpartum and also as measured on an EPDS scale at 60 days. Maternal satisfaction with postnatal care may be better with home visits (RR 1.36, 95% CI 1.14 to 1.62; three studies, 2368 women). There may be little to no difference in infant emergency health care visits or infant hospital readmissions (RR 1.15, 95% CI 0.95 to 1.38; three studies, 3257 women) or in exclusive breastfeeding at two weeks (RR 1.05, 95% CI 0.93 to 1.18; 1 study, 513 women).

Authors' conclusions: The evidence is very uncertain about the effect of home visits on maternal and neonatal mortality. Individualised care as part of a package of home visits probably improves depression scores at four months and increasing the frequency of home visits may improve exclusive breastfeeding rates and infant healthcare utilisation. Maternal satisfaction may also be better with home visits compared to hospital check-ups. Overall, the certainty of evidence was found to be low and findings were not consistent among studies and comparisons. Further well designed RCTs evaluating this complex intervention will be required to formulate the optimal package

Mobile phones and Apps

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doi: 10.1002/14651858.CD012909.pub2.

Birth and death notification via mobile devices: a mixed methods systematic review

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Abstract

Background: Ministries of health, donors, and other decision-makers are exploring how they can use mobile technologies to acquire accurate and timely statistics on births and deaths. These stakeholders have called for evidence-based guidance on this topic. This review was carried out to support World Health Organization (WHO) recommendations on digital interventions for health system strengthening.

Objectives: Primary objective: To assess the effects of birth notification and death notification via a mobile device, compared to standard practice. Secondary objectives: To describe the range of strategies used to implement birth and death notification via mobile devices and identify factors influencing the implementation of birth and death notification via mobile devices.

Search methods: We searched CENTRAL, MEDLINE, Embase, the Global Health Library, and POPLINE (August 2, 2019). We searched two trial registries (August 2, 2019). We also searched Epistemonikos for related systematic reviews and potentially eligible primary studies (August 27, 2019). We conducted a grey literature search using mHealthevidence.org (August 15, 2017) and issued a call for papers through popular digital health communities of practice. Finally, we conducted citation searches of included studies in Web of Science and Google Scholar (May 15, 2020). We searched for studies published after 2000 in any language.

SELECTION CRITERIA: For the primary objective, we included individual and cluster-randomised trials; cross-over and stepped-wedge study designs; controlled before-after studies, provided they have at least two intervention sites and two control sites; and interrupted time series studies. For the secondary objectives, we included any study design, either quantitative, qualitative, or descriptive, that aimed to describe current strategies for birth and death notification via mobile devices; or to explore factors that influence the implementation of these strategies, including studies of acceptability or feasibility. For the primary objective, we included studies that compared birth and death notification via mobile devices with standard practice. For the secondary objectives, we included studies of birth and death notification via mobile device as long as we could extract data relevant to our secondary objectives. We included studies of all cadres of healthcare providers, including lay health workers; administrative, managerial, and supervisory staff; focal individuals at the village or community level; children whose births were being notified and their parents/caregivers; and individuals whose deaths were being notified and their relatives/caregivers.

Data collection and analysis: For the primary objective, two authors independently screened all records, extracted data from the included studies and assessed risk of bias. For the analyses of the primary objective, we reported means and proportions, where appropriate. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence and we prepared a 'Summary of Findings' table. For the secondary objectives, two authors screened all records,

one author extracted data from the included studies and assessed methodological limitations using the WEIRD tool and a second author checked the data and assessments. We carried out a framework analysis using the Supporting the Use of Research Evidence (SURE) framework to identify themes in the data. We used the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) approach to assess our confidence in the evidence and we prepared a 'Summary of Qualitative Findings' table.
Main results: For the primary objective, we included one study, which used a controlled before-after study design. The study was conducted in Lao People's Democratic Republic and assessed the effect of using mobile devices for birth notification on outcomes related to coverage and timeliness of Hepatitis B vaccination. However, we are uncertain of the effect of this approach on these outcomes because the certainty of this evidence was assessed as very low. The included study did not assess resource use or unintended consequences. For the primary objective, we did not identify any studies using mobile devices for death notification. For the secondary objective, we included 21 studies. All studies were conducted in low- or middle-income settings. They focussed on identification of births and deaths in rural, remote, or marginalised populations who are typically under-represented in civil registration processes or traditionally seen as having poor access to health services. The review identified several factors that could influence the implementation of birth-death notification via mobile device. These factors were tied to the health system, the person responsible for notifying, the community and families; and include: - Geographic barriers that could prevent people's access to birth-death notification and post-notification services - Access to health workers and other notifiers with enough training, supervision, support, and incentives - Monitoring systems that ensure the quality and timeliness of the birth and death data - Legal frameworks that allow births and deaths to be notified by mobile device and by different types of notifiers - Community awareness of the need to register births and deaths - Socio-cultural norms around birth and death - Government commitment - Cost to the system, to health workers and to families - Access to electricity and network connectivity, and compatibility with existing systems - Systems that protect data confidentiality We have low to moderate confidence in these findings. This was mainly because of concerns about methodological limitations and data adequacy.
Authors' conclusions: We need more, well-designed studies of the effect of birth and death notification via mobile devices and on factors that may influence its implementation.

Matern Child Nutr. 2021 Oct;17(4):e13224.
doi: 10.1111/mcn.13224. Epub 2021 Aug 19.
Evaluation of mobile phone-based Positive Deviance/Hearth child undernutrition program in Cambodia
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Abstract
Child undernutrition in Cambodia is a persistent public health problem requiring low-cost and scalable solutions. Rising cellphone use in low-resource settings represents an opportunity to replace in-person counselling visits with phone calls; however, questions remain on relative effectiveness. Our objective was to evaluate the impact of two options for delivering a World Vision infant and young child feeding (IYCF) counselling programme: (1)

traditional Positive Deviance/Hearth (PDH) programme with in-person visits or (2) PDH with Interactive Voice Calling (PDH-IVC) which integrates phone calls to replace 62.5% of face-to-face interaction between caregivers and volunteers, compared to the standard of care (SOC). We conducted a longitudinal cluster-randomised controlled trial in 361 children 6-23 months. We used an adjusted difference-in-difference approach using baseline, midline (3 months) and endline (12 months) surveys to evaluate the impact on child growth among the three groups. At baseline, nearly a third of children were underweight, and over half were food insecure. At midline the PDH group and the PDH-IVC groups had improved weight-for-age z-scores (0.13 DID, p = 0.011; 0.13 DID, p = 0.02, respectively) and weight-for-height z-score (0.16 DID, p = 0.038; 0.24 DID, p = 0.002), relative to SOC. There were no differences in child height-for-age z-scores. At endline, the impact was sustained only in the PDH-IVC group for weight-for-age z-score (0.14 DID, p = 0.049), and the prevalence of underweight declined by 12.8 percentage points (p = 0.036), relative to SOC. Integration of phone-based IYCF counselling is a potentially promising solution to reduce the burden of in-person visits; however, the modest improvements suggest the need to combine it with other strategies to improve child nutrition.

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Decision-support tools via mobile devices to improve quality of care in primary healthcare settings

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Abstract

Background: The ubiquity of mobile devices has made it possible for clinical decision-support systems (CDSS) to become available to healthcare providers on handheld devices at the point-of-care, including in low- and middle-income countries. The use of CDSS by providers can potentially improve adherence to treatment protocols and patient outcomes. However, the evidence on the effect of the use of CDSS on mobile devices needs to be synthesized. This review was carried out to support a World Health Organization (WHO) guideline that aimed to inform investments on the use of decision-support tools on digital devices to strengthen primary healthcare.

Objectives: To assess the effects of digital clinical decision-support systems (CDSS) accessible via mobile devices by primary healthcare providers in the context of primary care settings.

Search methods: We searched CENTRAL, MEDLINE, Embase, Global Index Medicus, POPLINE, and two trial registries from 1 January 2000 to 9 October 2020. We conducted a grey literature search using mHealthevidence.org and issued a call for papers through popular digital health communities of practice. Finally, we conducted citation searches of included studies.

Selection criteria: Study design: we included randomized trials, including full-text studies, conference abstracts, and unpublished data irrespective of publication status or language of publication. Types of participants: we included studies of all cadres of healthcare providers, including lay health workers and other individuals (administrative, managerial, and supervisory staff) involved in the delivery of primary healthcare services using clinical

decision-support tools; and studies of clients or patients receiving care from primary healthcare providers using digital decision-support tools. Types of interventions: we included studies comparing digital CDSS accessible via mobile devices with non-digital CDSS or no intervention, in the context of primary care. CDSS could include clinical protocols, checklists, and other job-aids which supported risk prioritization of patients. Mobile devices included mobile phones of any type (but not analogue landline telephones), as well as tablets, personal digital assistants, and smartphones. We excluded studies where digital CDSS were used on laptops or integrated with electronic medical records or other types of longitudinal tracking of clients.
Data collection and analysis: A machine learning classifier that gave each record a probability score of being a randomized trial screened all search results. Two review authors screened titles and abstracts of studies with more than 10% probability of being a randomized trial, and one review author screened those with less than 10% probability of being a randomized trial. We followed standard methodological procedures expected by Cochrane and the Effective Practice and Organisation of Care group. We used the GRADE approach to assess the certainty of the evidence for the most important outcomes.
Main results: Eight randomized trials across varying healthcare contexts in the USA,. India, China, Guatemala, Ghana, and Kenya, met our inclusion criteria. A range of healthcare providers (facility and community-based, formally trained, and lay workers) used digital CDSS. Care was provided for the management of specific conditions such as cardiovascular disease, gastrointestinal risk assessment, and maternal and child health. The certainty of evidence ranged from very low to moderate, and we often downgraded evidence for risk of bias and imprecision. We are uncertain of the effect of this intervention on providers' adherence to recommended practice due to the very low certainty evidence (2 studies, 185 participants). The effect of the intervention on patients' and clients' health behaviours such as smoking and treatment adherence is mixed, with substantial variation across outcomes for similar types of behaviour (2 studies, 2262 participants). The intervention probably makes little or no difference to smoking rates among people at risk of cardiovascular disease but probably increases other types of desired behaviour among patients, such as adherence to treatment. The effect of the intervention on patients'/clients' health status and well-being is also mixed (5 studies, 69,767 participants). It probably makes little or no difference to some types of health outcomes, but we are uncertain about other health outcomes, including maternal and neonatal deaths, due to very low-certainty evidence. The intervention may slightly improve patient or client acceptability and satisfaction (1 study, 187 participants). We found no studies that reported the time between the presentation of an illness and appropriate management, provider acceptability or satisfaction, resource use, or unintended consequences.
Authors' conclusions: We are uncertain about the effectiveness of mobile phone-based decision-support tools on several outcomes, including adherence to recommended practice. None of the studies had a quality of care framework and focused only on specific health areas. We need well-designed research that takes a systems lens to assess these issues.

Newborn care

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Impact of early kangaroo mother care versus standard care on survival of mild-moderately unstable neonates <2000 grams: A randomised controlled trial

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Abstract

Background: Understanding the effect of early kangaroo mother care on survival of mild-moderately unstable neonates <2000 g is a high-priority evidence gap for small and sick newborn care.

Methods: This non-blinded pragmatic randomised clinical trial was conducted at the only teaching hospital in The Gambia. Eligibility criteria included weight <2000g and age 1-24 h with exclusion if stable or severely unstable. Neonates were randomly assigned to receive either standard care, including KMC once stable at >24 h after admission (control) versus KMC initiated <24 h after admission (intervention). Randomisation was stratified by weight with twins in the same arm. The primary outcome was all-cause mortality at 28 postnatal days, assessed by intention to treat analysis. Secondary outcomes included: time to death; hypothermia and stability at 24 h; breastfeeding at discharge; infections; weight gain at 28d and admission duration. The trial was prospectively registered at www.clinicaltrials.gov (NCT03555981).

Findings: Recruitment occurred from 23rd May 2018 to 19th March 2020. Among 1,107 neonates screened for participation 279 were randomly assigned, 139 (42% male [*n* = 59]) to standard care and 138 (43% male [*n* = 59]) to the intervention with two participants lost to follow up and no withdrawals. The proportion dying within 28d was 24% (34/139, control) vs. 21% (29/138, intervention) (risk ratio 0·84, 95% CI 0·55 - 1·29, *p* = 0·423). There were no between-arm differences for secondary outcomes or serious adverse events (28/139 (20%) for control and 30/139 (22%) for intervention, none related). One-third of intervention neonates reverted to standard care for clinical reasons.

Interpretation: The trial had low power due to halving of baseline neonatal mortality, highlighting the importance of implementing existing small and sick newborn care interventions. Further mortality effect and safety data are needed from varying low and middle-income neonatal unit contexts before changing global guidelines.

*** Indian J Pediatr. 2022 May;89(5):484-489.
doi: 10.1007/s12098-022-04145-9. Epub 2022 Mar 4.

Mother-Newborn Care Unit (MNCU) Experience in India: A Paradigm Shift in Care of Small and Sick Newborns

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Abstract

While a Cochrane review (2016) showed that kangaroo mother care (KMC) initiated after clinical stabilization reduces mortality by 40%, evidence of the effect of initiating KMC immediately after birth without waiting for babies to become stable was unavailable until recently. This research gap was addressed by a multicountry, randomized, controlled trial

co-ordinated by WHO. This trial was conducted in five hospitals in Ghana, India, Malawi, Nigeria, and Tanzania. Implementation of this trial led to development of the "mother-newborn care unit (MNCU)." Mother-newborn care unit or mother-newborn intensive care unit (M-NICU) is a facility where sick and small newborns are cared with their mothers 24 × 7 with all facilities of level II newborn care and provision for postnatal care to mothers. The mother is not a mere visitor, but she has her bed inside the special newborn care unit (SNCU)/newborn intensive care unit (NICU) and as a resident of MNCU, becomes an active caregiver and is involved in continuum of neonatal care. The study results show that intervention babies in MNCU had 25% less mortality at 28 d of life, 35% less incidence of hypothermia, and 18% less suspected sepsis as compared to control babies cared in conventional NICU. World Health Organization is in the process of reviewing the current recommendations on care of preterm or LBW newborns considering new evidence that has become available. However, it would require national policy change to permit mother and surrogate in SNCU/NICU 24 × 7, making the concept of zero-separation a reality.

Am J Trop Med Hyg. 2021 Dec 20;106(3):945-952.
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Effect of Community-Initiated Kangaroo Mother Care on Fecal Biomarkers of Gut Function in Low Birth Weight Infants in North India: A Randomized Clinical Trial

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Abstract

This individually randomized trial was conducted to estimate the effect of promoting community-initiated Kangaroo Mother Care (ciKMC) in low birth weight (LBW) infants on gut inflammation and permeability. Participants included 200 stable LBW infants (weighing 1,500-2,250 g) in North India enrolled between May and October 2017. The ciKMC intervention included promotion and support of continuous skin-to-skin contact and exclusive breastfeeding through home visits. The mothers in the intervention arm were supported to practice ciKMC until 28 days after birth, i.e., the neonatal period, or till the baby wriggled out of KMC position, if earlier. Infant stool specimens were collected during the first week of birth, and within 1 week after end of the neonatal period. Concentrations of fecal neopterin (nmol/L), myeloperoxidase (ng/mL), and alpha-1-antitrypsin (µg/mL) were determined using ELISA, and composite enteric enteropathy (EE) score at the end of the neonatal period was calculated by principal component analysis. We did not find any substantial difference in means between the ciKMC and control arm infants in the log-transformed values of neopterin (0.03; 95% CI -0.15 to 0.21), myeloperoxidase (0.28; 95% CI -0.05 to 0.61) and alpha-1-antitrypsin (0.02; 95% CI -0.30 to 0.34). The mean (SD) composite EE score was 13.6 (7.5) in the ciKMC and 12.4 (8.3) in the control arm infants, and the adjusted difference in means was, 0.4 (95% CI -1.8 to 2.7). Our findings suggest that the promotion of ciKMC did not affect gut inflammation and permeability in our target population of LBW infants in North India.

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Health equity impact of community-initiated kangaroo mother care: a randomized controlled trial

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Abstract

Background: Kangaroo mother care (KMC) can substantially enhance overall survival of low birthweight babies. In a large randomized controlled trial, we recently showed that supporting mothers to provide community initiated KMC (ciKMC) can reduce mortality among infants up to 180 days of life by 25% (hazard ratio (HR) 0.75). With the current analysis, we aimed to explore if ciKMC promotion leads to increased inequity in survival.

Methods: In the trial we randomized 8402 low birthweight babies to a ciKMC (4480 babies) and a control (3922 babies) arm, between 2015 and 2018 in Haryana, India. We estimated the difference in concentration indices, which measure inequality, between babies in the ciKMC and control arms for survival until 180 days of life. Further, we compared the effect of ciKMC promotion across subgroups defined by socioeconomic status, caste, maternal literacy, infant's sex, and religion.

Results: Our intervention did not increase survival inequity, as the concentration index in the ciKMC arm of the trial was 0.05 (95% CI -0.07 to 0.17) lower than in the control arm. Survival impact was higher among those belonging to the lower two wealth quintiles, those born to illiterate mothers and those belonging to religions other than Hindu.

Conclusions: We found that ciKMC promotion did not increase inequity in survival associated with wealth. The beneficial impact of ciKMC tended to be larger among vulnerable groups. Supporting mothers to provide KMC at home to low birthweight babies will not increase and could indeed reduce inequities in infant survival.

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Outcomes of a Telephonic Postnatal Intervention for Mothers and Babies in Mopani District, Limpopo, South Africa

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Abstract

Background: The postnatal period is a critical period for the health of both mother and infant. Studies show that postnatal care reduces neonatal mortality and other adverse mother and child health outcomes. While the World Health Organization recommends four postnatal care contacts, South African guidelines only specify three, excluding a 7-14-day post-birth contact. This study aimed to assess whether a telephonic contact at 7-14 days following delivery had any effect on use of additional postnatal services.

Methods: A randomized controlled trial design was used to address the study objectives. Two groups of new mothers were randomly allocated to either receive the 7-14-day telephonic contact or not from a research nurse. Data for this study was collected at Maphutha L Malatjie Hospital (MLMH). Descriptive analysis was performed first, then a

multivariable logistic regression analysis was conducted to assess the factors associated with access to other health care services.
Results: A total of 882 mothers were recruited, 854 (97%) were classified as high risk, 28 (3%) were classified as low risk. 417 (49%) of the high risk received the 7-14-day call (intervention group) whilst the remainder of 437 (51%) from the high risk plus all mothers classified as low risk (28) did not receive the call (control group). 686 (78%) of all mothers received the 3 month follow up call. The call showed that 17 mothers from the control group and 10 mothers from the intervention group accessed other healthcare services. We find that hypertension (3.28; 1.06 -10.10), mental health risk (2.82; 1.25 -6.38), PV bleeding during pregnancy (18.33; 1.79-187.61), problem during labor (4.40; 1.280-15.13) were positively associated with access to other health services, with statistically significant associations (*p*-value < 0.05). We found statistically insignificant associations between receiving the 7-14-day call and accessing other health care services.
Conclusion: The 7-14-day call had no statistically significant impact on access to other health services, however, high levels of satisfaction with the call may point to an unmet need for care at this time. It is important to investigate other innovative solutions to postnatal care improvement in South Africa.

J Glob Health. 2022 Feb 5;12:04003.
doi: 10.7189/jogh.12.04003. eCollection 2022.
Universal home visits improve male knowledge and attitudes about maternal and child health in Bauchi State, Nigeria: Secondary outcome analysis of a stepped wedge cluster randomised controlled trial
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Abstract
Background: The World Health Organization recommends increased male involvement to improve maternal and newborn health in low- and middle-income countries, but few studies have measured the impact of male-engagement interventions on targeted men. A trial of universal home visits to pregnant women and their spouses in Nigeria improved maternal and child health outcomes. This analysis examines the impact of the visits on male spouses.
Methods: In Toro Local Government Area in Bauchi State, Nigeria, we randomly allocated eight wards into four waves, beginning the intervention at one-year intervals. The intervention comprised two-monthly evidence-based home visits to discuss local risk factors for maternal and child health with all pregnant women and their male spouses. Measured secondary outcomes of the intervention in the men included knowledge about danger signs in pregnancy and childbirth, beliefs about heavy work in pregnancy, discussion with their wives about pregnancy and childbirth, knowledge about causes and intentions about management of childhood diarrhoea, and views about childhood immunisation. The analysis compared outcomes between men in visited wards (intervention group) and pre-intervention wards (control group), using a cluster *t* test. Generalised linear mixed modelling accounted for the effect of socio-economic differences on the measured impact.
Results: The analysis included 6931 men in the intervention group and 9434 in the control group. More men in the intervention group knew four or more danger signs in pregnancy

(risk difference (RD) = 0.186, 95% confidence interval (CI) = 0.044 to 0.327), and three danger signs in childbirth (RD = 0.091, 95%CI = 0.013 to 0.170), thought pregnant women should reduce heavy work before the third trimester (RD = 0.088, 95% CI = 0.015 to 0.162), and had discussed pregnancy and childbirth with their spouse (RD = 0.157, 95% CI = 0.026 to 0.288). More knew correct management of childhood diarrhoea with fluids and feeding (RD = 0.300, 95% CI = 0.203 to 0.397) and less would give a child medicine to stop diarrhoea (RD = 0.206, 95% CI = 0.125 to 0.287). Socio-economic differences did not explain the effect of the intervention on any of the outcomes.
Conclusion: Universal home visits improved knowledge of male spouses about maternal and child health, which could contribute to improved maternal and child outcomes.

Neonatal sepsis

Eur J Pediatr. 2022 Jan;181(1):369-381.
doi: 10.1007/s00431-021-04194-w. Epub 2021 Aug 5.
The effect of exchange transfusion on mortality in neonatal sepsis: a meta-analysis
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Abstract
Although antimicrobials are the cornerstone of neonatal sepsis management, adjunctive therapies are required to improve outcomes. The aim of our study was to evaluate the effect of exchange transfusion (ET) on mortality (primary outcome) in neonatal sepsis, as well as on immunoglobulin, complement and neutrophil levels and assess its complications (secondary outcomes). Databases searched include PubMed, NCBI, Google Scholar, CINHAL, Ovid and Scopus. Randomized controlled trials (RCTs), controlled observational studies (COSs) and uncontrolled observational studies (UOSs) reporting mortality data from using ET in neonatal sepsis were included. Studies with additional interventions, non-septic ET indications and populations aged > 28 days were excluded. Data extracted include demographics, features of study, sepsis and ET, as well as mortality rates, immunological and laboratory changes and complications. Data was meta-analysed and displayed using forest plots. The meta-analysis of 14 studies (3 RCTs, 11 COSs) revealed a mortality benefit in septic neonates who underwent ET-RR 0.72 (CI 0.61-0.86, p = 0.01) and a significant increase in pooled immunological parameters (immunoglobulin, complement levels) (SMD 1.13, [0.25, 2.02], p = 0.02) and neutrophil levels (SMD 1.07 [0.04, 2.11], p = 0.03) compared to controls. The descriptive analysis of 9 UOSs revealed thrombocytopenia as the most frequently reported complication (n = 48). Moderate-high risk of bias was largely due to inadequate sample sizes and follow-up durations.Conclusion: Currently, the use of ET in neonatal sepsis is not directly recommended due to low certainty of evidence, inadequate power and moderate-high risk of bias and heterogeneity

BMC Health Serv Res. 2021 Nov 19;21(1):1249.
doi: 10.1186/s12913-021-06971-7.
Cost and consequences of using 7.1 % chlorhexidine gel for newborn umbilical cord care in Kenya

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Abstract

Background: Omphalitis is an important contributor to neonatal mortality in Kenya. Chlorhexidine digluconate 7.1 % w/w (CHX; equivalent to 4 % w/w chlorhexidine) was identified as a life-saving commodity for newborn cord care by the United Nations and is included on World Health Organization and Kenyan Essential Medicines Lists. This pilot study assessed the potential resource savings and breakeven price of implementing CHX for neonatal umbilical cord care versus dry cord care (DCC) in Kenya.

Methods: We employed a cost-consequence model in a Kenyan birth cohort. Firstly, the number of omphalitis cases and cases avoided by healthcare sector were estimated. Incidence rates and treatment effect inputs were calculated from a Cochrane meta-analysis of randomised clinical trials (RCTs) (base case) and 2 other RCTs. Economic outcomes associated with omphalitis cases avoided were determined, including direct, indirect and total cost of care associated with omphalitis, resource use (outpatient visits and bed days) and societal impact (caregiver workdays lost). Costs and other inputs were sourced from literature and supplemented by expert clinical opinion/informed inputs, making necessary assumptions.

Results: The model estimated that, over 1 year, ~ 23,000 omphalitis cases per 500,000 births could be avoided through CHX application versus DCC, circumventing ~ 13,000 outpatient visits, ~ 43,000 bed days and preserving ~ 114,000 workdays. CHX was associated with annual direct cost savings of ~ 590,000 US dollars (USD) versus DCC (not including drug-acquisition cost), increasing to ~ 2.5 million USD after including indirect costs (productivity, notional salary loss). The most-influential model parameter was relative risk of omphalitis with CHX versus DCC. Breakeven analysis identified a budget-neutral price for CHX use of 1.18 USD/course when accounting for direct cost savings only, and 5.43 USD/course when including indirect cost savings. The estimated breakeven price was robust to parameter input changes. DCC does not necessarily represent standard of care in Kenya; other, potentially harmful, approaches may be used, meaning cost savings may be understated.

Conclusions: Estimated healthcare cost savings and potential health benefits provide compelling evidence to implement CHX for umbilical cord care in Kenya. We encourage comprehensive data collection to make future models and estimates of impacts of upscaling CHX use more robust.

Low birth weight and prematurity

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Impact of Kangaroo Care on Premature Infants' Oxygenation: Systematic Review

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Free article

Abstract

Introduction: Kangaroo care (KC) is defined by the World Health Organization as a method of care consisting in putting premature infants or newborns in skin-to-skin contact with their parents. KC is an effective method of promoting health and well-being of infants and their families. Physiological stability during KC has been widely analyzed, however with controversial results.

Methods: A systematic review was conducted. Electronic databases searched included MEDLINE, Embase, CINAHL, and Scopus. Two authors independently reviewed and extracted information using a data extraction form. The methodological quality of the observational studies was assessed using "STROBE" and the "Cochrane Collaboration tool" for randomized controlled trials. The physiological monitoring parameters included were heart rate (HR), arterial oxygen saturation (SpO2), regional cerebral oxygen saturation (rScO2), and fractional oxygen extraction (FtOE).

Results: A total of 345 articles were identified. First, 302 articles were excluded by title and then 34 articles after full-text analysis. Finally, a total of 25 studies were included. Physiological parameters monitored (HR, SpO2, rScO2, and FtOE) showed no significant changes at different study periods: pre-KC, during KC, and post-KC.

Conclusions: We conclude that stable preterm infants receiving or not respiratory support show no significant differences in HR, SpO2, FtOE during KC compared to routine incubator care. rScO2 remains stable during KC with slight upward trend. Further studies with a higher level of methodological quality are needed to confirm these findings.

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Antenatal dexamethasone for late preterm birth: A multi-centre, two-arm, parallel, double-blind, placebo-controlled, randomized trial

WHO ACTION Trials Collaborators

Abstract

Background: There is currently insufficient evidence on the safety and efficacy of antenatal corticosteroids in preventing mortality and severe morbidity amongst late preterm newborns in low-resource countries.

Methods: We conducted a double-blind, randomized trial in four hospitals in India between 26 December 2017 to 21 May 2020. Pregnant women at risk of imminent preterm birth between 34 weeks 0 days and 36 weeks 0 days of gestation were recruited. Women were randomly assigned (1:1) to a course of 6 mg intramuscular dexamethasone or an identical placebo. All trial participants, research staff and outcome assessors were masked to allocation. Primary outcomes were neonatal death, any baby death (stillbirth or neonatal death), severe neonatal respiratory distress and possible maternal bacterial infection. The study was registered with ANZCTR (ACTRN12617001494325) and CTRI (CTRI/2017/05/008721).

Findings: We randomized 782 women, 391 to each arm. Neonatal death occurred in 11 of 412 liveborn babies (2.7%) in the dexamethasone group and 12 of 425 liveborn babies (2.8%) in the placebo group (RR 0.95; 95% CI 0.42-2.12). Any baby death occurred in 16 of 417 infants (3.8%) in the dexamethasone group and 19 of 432 infants (4.4%) in the placebo group (RR 0.87; 95% CI 0.45-1.67). Severe neonatal respiratory distress was infrequent in both groups

(0.8% vs 0.5%; RR 1.56; 95% CI 0.26-9.29). Possible maternal bacterial infection did not differ between groups (2.3% vs. 3.8%, RR 0.60; 95% CI 0.27-1.35). Fewer neonates in the dexamethasone group required resuscitation at birth (RR 0.38, CI 0.15-0.97). Other secondary outcomes were similar in the two arms. The trial was stopped due to lower than expected prevalence of primary outcomes and slow recruitment.
Interpretation: Antenatal dexamethasone did not result in a reduction in neonatal death, stillbirth or neonatal death, or severe neonatal respiratory distress in this trial. The overall trend of effects suggests that potential benefit of dexamethasone in late preterm cannot be excluded, and further trials are required.

JAMA Pediatr. 2021 Jun 1;175(6):e206826.
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Assessment of Postnatal Corticosteroids for the Prevention of Bronchopulmonary Dysplasia in Preterm Neonates: A Systematic Review and Network Meta-analysis

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Abstract

Importance: The safety of postnatal corticosteroids used for prevention of bronchopulmonary dysplasia (BPD) in preterm neonates is a controversial matter, and a risk-benefit balance needs to be struck.
Objective: To evaluate 14 corticosteroid regimens used to prevent BPD: moderately early-initiated, low cumulative dose of systemic dexamethasone (MoLdDX); moderately early-initiated, medium cumulative dose of systemic dexamethasone (MoMdDX); moderately early-initiated, high cumulative dose of systemic dexamethasone (MoHdDX); late-initiated, low cumulative dose of systemic dexamethasone (LaLdDX); late-initiated, medium cumulative dose of systemic dexamethasone (LaMdDX); late-initiated, high cumulative dose of systemic dexamethasone (LaHdDX); early-initiated systemic hydrocortisone (EHC); late-initiated systemic hydrocortisone (LHC); early-initiated inhaled budesonide (EIBUD); early-initiated inhaled beclomethasone (EIBEC); early-initiated inhaled fluticasone (EIFLUT); late-initiated inhaled budesonide (LIBUD); late-initiated inhaled beclomethasone (LIBEC); and intratracheal budesonide (ITBUD).
Data sources: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, World Health Organization's International Clinical Trials Registry Platform (ICTRP), and CINAHL were searched from inception through August 25, 2020.
Study selection: In this systematic review and network meta-analysis, the randomized clinical trials selected included preterm neonates with a gestational age of 32 weeks or younger and for whom a corticosteroid regimen was initiated within 4 weeks of postnatal age. Peer-reviewed articles and abstracts in all languages were included.
Data extraction and synthesis: Two independent authors extracted data in duplicate. Network meta-analysis used a bayesian model.
Main outcomes and measures: Primary combined outcome was BPD, defined as oxygen requirement at 36 weeks' postmenstrual age (PMA), or mortality at 36 weeks' PMA. The secondary outcomes included 15 safety outcomes.
Results: A total of 62 studies involving 5559 neonates (mean [SD] gestational age, 26 [1] weeks) were included. Several regimens were associated with a decreased risk of BPD or mortality, including EHC (risk ratio [RR], 0.82; 95% credible interval [CrI], 0.68-0.97); EIFLUT

(RR, 0.75; 95% CrI, 0.55-0.98); LaHdDX (RR, 0.70; 95% CrI, 0.54-0.87); MoHdDX (RR, 0.64; 95% CrI, 0.48-0.82); ITBUD (RR, 0.73; 95% CrI, 0.57-0.91); and MoMdDX (RR, 0.61; 95% CrI, 0.45-0.79). Surface under the cumulative ranking curve (SUCRA) value ranking showed that MoMdDX (SUCRA, 0.91), MoHdDX (SUCRA, 0.86), and LaHdDX (SUCRA, 0.76) were the 3 most beneficial interventions. ITBUD (RR, 4.36; 95% CrI, 1.04-12.90); LaHdDX (RR, 11.91; 95% CrI, 1.64-44.49); LaLdDX (RR, 6.33; 95% CrI, 1.62-18.56); MoHdDX (RR, 4.96; 95% CrI, 1.14-14.75); and MoMdDX (RR, 3.16; 95% CrI, 1.35-6.82) were associated with more successful extubation from invasive mechanical ventilation. EHC was associated with a higher risk of gastrointestinal perforation (RR, 2.77; 95% CrI, 1.09-9.32). MoMdDX showed a higher risk of hypertension (RR, 3.96; 95% CrI, 1.10-30.91). MoHdDX had a higher risk of hypertrophic cardiomyopathy (RR, 5.94; 95% CrI, 1.95-18.11).
Conclusions and relevance: This study suggested that MoMdDX may be the most appropriate postnatal corticosteroid regimen for preventing BPD or mortality at a PMA of 36 weeks, albeit with a risk of hypertension. The quality of evidence was low.

Jaundice

J Trop Pediatr. 2022 Feb 3;68(2):fmac023.
doi: 10.1093/tropej/fmac023.
The Effect of Breastfeeding and an Intensive Breast Milk Nutritional Support Program on Hospitalization Rates for Hyperbilirubinemia in Term Newborns: An Open Randomized Controlled Trial
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Objective: The aim of this study was to determine the effect of breastfeeding and intensive breast milk nutritional support program (IBNSP) on hospitalization rates for hyperbilirubinemia in normal term newborns.
Methods: This study's sample consisted of 68 newborn infants (experimental group: 34; control group: 34) born at a university hospital from October 2020 to April 2021. Five steps of breastfeeding and IBNSP were administered to the experimental group for the first 48 h after birth. This program starts at the postpartum first hour and continues until the 48th hour. It includes face-to-face training, practical support on breastfeeding, and one-to-one demonstration and practice methods. The control group received the standard care recommended by the World Health Organization. Both groups' bilirubin levels were measured 24 and 72 h after birth. Participants in both groups were hospitalized for risky (according to bilirubin values) situations. The groups' bilirubin levels and hospitalization rates for hyperbilirubinemia were compared.
Results: There was no statistically significant difference between the experimental (5.19 ± 1.27) and the control (5.83 ± 1.52) groups' bilirubin levels at 24 h after birth, (t = -1.881, p = 0.064); however, the control group infants (12.03 ± 3.67 mg/dl) had higher bilirubin levels than the infants in the experimental group 72 h after birth (9.55 ± 2.82 mg/dl) (t = -3.122, p = 0.003). The experimental group's hospitalization rate for hyperbilirubinemia (n: 1, 2.9%) was lower than the control group's rate (n: 8, 23.5%), and this difference was statistically significant (X2 = 6.275, p = 0.014).

Conclusions: Breastfeeding and IBNSP effectively prevent hospitalization for hyperbilirubinemia and reduce newborns' bilirubin levels.

Nutrition

(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

(See also Vitamin A)

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A randomized trial of iron- and zinc-biofortified pearl millet-based complementary feeding in children aged 12 to 18 months living in urban slums

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Abstract

Background & aims: Biofortification of staple crops with higher levels of micronutrients via traditional breeding methods is a sustainable strategy and can possibly complement fortification and other interventions to target micronutrient deficiencies in low resource settings, particularly among vulnerable populations such as children. We aimed to determine if iron- and zinc-biofortified pearl millet (FeZnPM, Dhanashakti, ICTP-8203Fe)-based complementary feeding improves nutritional status, including iron biomarkers and growth, in children living in urban slums of Mumbai.

Methods: We conducted a randomized controlled trial of FeZnPM among 223 children aged 12-18 months who were not severely anemic at baseline (hemoglobin ≥9.0 g/dL). Children were randomized to receive either FeZnPM or conventional non-biofortified pearl millet (CPM) daily for 9 months. Iron status (hemoglobin, serum ferritin), plasma zinc, and anthropometric indicators (length, weight, mid-upper arm circumference, triceps and subscapular skinfolds) were evaluated at enrollment and throughout the trial. World Health Organization (WHO) anthropometric z-scores were calculated using WHO growth standards. Primary outcomes were hemoglobin and serum ferritin concentrations, and growth, defined as WHO z-scores. An intent to treat approach was used for analyses. We used the Hodges-Lehmann-Sen test to assess the change in primary outcomes between baseline and the last visit and report corresponding 95% confidence intervals.

Results: At baseline, 67.7% of children were anemic (hemoglobin <11.0 g/dL) and 59.6% were iron deficient (serum ferritin <12.0 µg/L). FeZnPM did not significantly increase iron biomarkers or improve growth, compared to CPM. In subgroup analyses, FeZnPM improved hemoglobin concentrations in male children, and in children with iron deficiency or iron depletion (serum ferritin <25.0 µg/L) at baseline, relative to CPM.

Conclusions: Daily consumption of FeZnPM-based complementary foods did not significantly impact iron and zinc status or growth in children living in Mumbai's urban

slums. However, the intervention significantly improved hemoglobin concentrations among male children and among individuals who were iron-deficient or iron-depleted at baseline.

Lipid-based nutrition supplements

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Characteristics that modify the effect of small-quantity lipid-based nutrient supplementation on child growth: an individual participant data meta-analysis of randomized controlled trials

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Abstract

Background: Meta-analyses show that small-quantity lipid-based nutrient supplements (SQ-LNSs) reduce child stunting and wasting. Identification of subgroups who benefit most from SQ-LNSs may facilitate program design.

Objectives: We aimed to identify study-level and individual-level modifiers of the effect of SQ-LNSs on child growth outcomes.

Methods: We conducted a 2-stage meta-analysis of individual participant data from 14 randomized controlled trials of SQ-LNSs provided to children 6-24 mo of age (n = 37,066). We generated study-specific and subgroup estimates of SQ-LNS compared with control and pooled the estimates using fixed-effects models. We used random-effects meta-regression to examine study-level effect modifiers. In sensitivity analyses, we examined whether results differed depending on study arm inclusion criteria and types of comparisons.

Results: SQ-LNS provision decreased stunting (length-for-age z score < -2) by 12% (relative reduction), wasting [weight-for-length (WLZ) z score < -2] by 14%, low midupper arm circumference (MUAC) (<125 mm or MUAC-for-age z score < -2) by 18%, acute malnutrition (WLZ < -2 or MUAC < 125 mm) by 14%, underweight (weight-for-age z score < -2) by 13%, and small head size (head circumference-for-age z score < -2) by 9%. Effects of SQ-LNSs generally did not differ by study-level characteristics including region, stunting burden, malaria prevalence, sanitation, water quality, duration of supplementation, frequency of contact, or average compliance with SQ-LNS. Effects of SQ-LNSs on stunting, wasting, low MUAC, and small head size were greater among girls than among boys; effects on stunting, underweight, and low MUAC were greater among later-born (than among firstborn) children; and effects on

wasting and acute malnutrition were greater among children in households with improved (as opposed to unimproved) sanitation.
Conclusions: The positive impact of SQ-LNSs on growth is apparent across a variety of study-level contexts. Policy-makers and program planners should consider including SQ-LNSs in packages of interventions to prevent both stunting and wasting.

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

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Impact of supplementation with milk-cereal mix during 6-12 months of age on growth at 12 months: a 3-arm randomized controlled trial in Delhi, India

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Abstract
Background: A large proportion of infants in low- and middle-income countries are stunted. These infants are often fed complementary foods that are low-quality, primarily in terms of protein and micronutrients.
Objectives: We aimed to test 2 milk-cereal mixes supplemented with modest and high amounts of protein during 6-12 mo of age, compared with no supplementation, for their effect on length-for-age z score (LAZ) at 12 mo of age.
Methods: Eligible infants (6 mo plus ≤29 d) were randomly assigned to either of the 2 interventions (modest- and high-protein) or a no supplement group. The milk-cereal mixes provided ∼125 kcal, 30%-45% energy from fats, and 80%-100% RDA of multiple micronutrients (MMN). The modest-protein group received 2.5 g protein [protein energy ratio (PER): 8%; 0.75 g from milk source] and the high-protein group received 5.6 g protein (PER: 18%, 1.68 g from milk source). One packet was given daily for 180 d. Counseling on continued breastfeeding and optimal infant-care practices was provided to all.
Results: We enrolled 1548 infants (high-protein: n = 512; modest-protein: n = 519; and no supplement: n = 517). Compared with the no supplement group, there was an improvement in LAZ [adjusted mean difference (MD): 0.08; 95% CI: 0.01, 0.15], weight-for-age z score (MD: 0.12; 95% CI: 0.06, 0.19), weight-for-length z score (MD: 0.11; 95% CI: 0.02, 0.19), and midupper arm circumference z score (MD: 0.10; 95% CI: 0.02, 0.18) in the high-protein group at 12 mo of age. No significant differences for these anthropometric indicators were noted between the modest-protein and no supplement groups or between the high- and modest-protein groups.
Conclusions: Cereal mixes with higher amounts of milk-based protein and MMN may lead to improvement in linear growth and other anthropometric indexes in infants, compared with no supplementation.

Breastfeeding

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Effect of maternal nutrition education on early initiation and exclusive breast-feeding practices in south Ethiopia: a cluster randomised control trial

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Abstract

Introduction: Optimal breast-feeding practices make a major contribution to the promotion of healthy growth and development through much prevention of diarrheal and respiratory diseases which majorly cause morbidity and mortality in under-five children. However, breast-feeding practices remain suboptimality in Ethiopia. *Objective:* The study objective was to determine the effect of maternal nutrition education on early initiation and exclusive breast-feeding practice in the Hawela Tulla sub-city. *Methods:* A cluster randomised, parallel-group, single-blinded trial was used. About 310 pregnant women (155 for the intervention group and 155 for the control group) were included. *Result:* An early initiation of breast-feeding was significantly higher among women who received breast-feeding education than those who did not receive (104(72·7 %) *v.* 85(59·9 %), *P* = 0·022) and exclusive breast-feeding practice was also significantly higher among women who received breast-feeding education than those who did not receive (106(74·1 %) *v.* 86(60·6 %), *P* = 0·015). Breast-feeding education [AORs 1·55, 95 % CI (1·02, 2·36)], institutional delivery [AOR 2·29, 95 % CI (1·21, 4·35)], vaginal delivery [AOR 2·85, 95 % CI (1·61, 5·41)] and pre-lacteal feeding [AOR 0·47, 95 % CI (0·25, 0·85)] were predictors of early initiation of breast-feeding. Breast-feeding education [AOR 1·72, 95 % CI (1·12, 2·64)] and institutional delivery [AOR 2·36, 95 % CI (1·28, 4·33)] were also determinants of exclusive breast-feeding practices. *Conclusion:* Breast-feeding education improved early initiation of breast-feeding and exclusive breast-feeding practices. Providing sustained education to women regarding early initiation and exclusive breast-feeding practice should be strengthened.

BMC Pregnancy Childbirth. 2022 Feb 16;22(1):132.
doi: 10.1186/s12884-022-04394-8.

Effectiveness of a group educational intervention - prolact - in primary care to promote exclusive breastfeeding: a cluster randomized clinical trial

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Abstract

Background: The rates of exclusive breastfeeding at 6 months in Spain are far from recommended by the World Health Organization, which is 50% by 2025. Evidence of the effectiveness of group interventions in late postpartum is limited. The objective of this study was to evaluate the effectiveness of the PROLACT group educational intervention for increasing the proportion of mother-child dyads with exclusive breastfeeding at 6 months compared to the usual practice in primary care.

Method: Multicentre cluster randomized clinical trial. A total of 434 mother-child dyads who breastfed exclusively in the first 4 weeks of the children's life and agreed to participate were

included. The main outcome was exclusive breastfeeding at 6 months. Secondary variables were type of breastfeeding, reasons for abandonment, degree of adherence and satisfaction with the intervention. To study the effectiveness, the difference in the proportions of dyads with exclusive breastfeeding at 6 months was calculated, and the relative risk (RR) and number needed to treat (NNT) were calculated with their 95% CIs. To study the factors associated with the maintenance of exclusive breastfeeding at 6 months, a multilevel logistic regression model was fitted. All analyses were performed to intention to treat.
Results: The percentage of dyads with exclusive breastfeeding at 6 months was 22.4% in the intervention group and 8.8% in the control group. PROLACT intervention obtained an RR =2.53 (95% CI: 1.54-4.15) and an NNT = 7 (95%CI: 5-14). The factors associated with exclusive breastfeeding at 6 months were the PROLACT intervention, OR = 3.51 (95%CI: 1.55-7.93); age > 39 years, OR = 2.79 (95%CI: 1.02-7.6); previous breastfeeding experience, OR = 2.61 (95%CI: 1.29-5.29); income between 500 and 833.33 €, OR = 3.52 (95%CI 1.47-8.47).); planning to start work before the infant was 6 months old, OR = 0.35 (0.19-0.63) .
Conclusions: The PROLACT intervention in primary care is more effective than the usual practice for maintaining exclusive breastfeeding at 6 months, and can therefore be considered evidence-based practice for implementation in standard practice.

Oncology

(see also HIV – management of HIV related conditions)

J Oral Biol Craniofac Res. 2021 Jul-Sep;11(3):373-378.
doi: 10.1016/j.jobcr.2021.04.001. Epub 2021 Apr 12.
Assessing the topical application efficiency of two biological agents in managing chemotherapy-induced oral mucositis in children: A randomized clinical trial
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Abstract
Background: oral mucositis is one of the most annoying complications of chemotherapy. This randomized clinical trial aimed to assess the efficiency of Aloe Vera and Olive Oil in managing chemotherapy-induced oral mucositis.
Methods: 36 children between 6 and 9 years and suffering from grade 3 or 4 oral mucositis, according to the World Health Organization (W.H.O.) scale, were enrolled in this clinical trial. Participants were separated into three groups to treat their mucositis using Aloe Vera, Olive Oil, or sodium bicarbonate. Nurses administrated the agents four times daily with sponge sticks. Two blinded investigators examined the oral mucosa after ten days.
Results: Both Aloe Vera and Olive Oil significant differences in the management of chemotherapy-induced oral mucositis compared to sodium bicarbonate treatments.

Ophthalmology and optometry

Cochrane Database Syst Rev. 2022 May 27;5(5):CD014617.

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Antibiotic prophylaxis for corneal abrasion

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Abstract

Background: Corneal abrasion is a common disorder frequently faced by ophthalmologists, emergency physicians, and primary care physicians. Ocular antibiotics are one of the management options for corneal abrasion. A comprehensive summary and synthesis of the evidence on antibiotic prophylaxis in traumatic corneal abrasion is thus far unavailable, therefore we conducted this review to evaluate the current evidence regarding this important issue.

Objectives: To assess the safety and efficacy of topical antibiotic prophylaxis following corneal abrasion. Our objectives were 1) to investigate the incidence of infection with antibiotics versus placebo or alternative antibiotics in people with corneal abrasion; and 2) to investigate time to clinical cure, defined as complete healing (re-epithelialization) of the epithelium, with antibiotics versus placebo or alternative antibiotics in people with corneal abrasion.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register; 2021, Issue 4), Ovid MEDLINE, Embase.com, PubMed, the Latin American and Caribbean Health Sciences Literature database (LILACS), ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We did not use any date or language restrictions in the electronic search for trials. We last searched the electronic databases on 25 April 2021.

Selection criteria: We included randomized controlled trials (RCTs) comparing antibiotic with another antibiotic or placebo in children and adults with corneal abrasion due to any cause.

Data collection and analysis: We used standard Cochrane methodology and assessed the certainty of the body of evidence for the prespecified outcomes using the GRADE classification.

Main results: Our search of the electronic databases yielded 8661 records. We screened 7690 titles and abstracts after removal of duplicates. We retrieved 32 full-text reports for further review. We included two studies that randomized a total of 527 eyes of 527 participants in the review. One study was conducted in Denmark, and one was conducted in India. The two studies did not examine most of our prespecified primary and secondary outcomes. The first study was a parallel-group RCT comparing chloramphenicol ocular ointment with fusidic acid ocular gels (frequency was not clearly reported). This study enrolled 153 participants older than 5 years of age with corneal abrasion in Denmark with a one-day follow-up duration. No participants had secondary infection in the fusidic acid group, whereas three (4.1%) participants in the chloramphenicol group had a slight reaction (risk ratio [RR] 0.15, 95% confidence interval [CI] 0.01 to 2.79; 144 participants; very low certainty evidence). Thirty-one (44.3%) participants in the fusidic acid arm and 34 (46.6%) participants in the chloramphenicol arm were cured (defined as the area of abrasion zero and no infection) at day 1 (RR 0.94, 95% CI 0.65 to 1.34; 144 participants; very low certainty evidence). Without providing specific data, the study reported that the degree of pain was not affected by the interventions received. The most common adverse events reported were itching and discomfort of the eye, which occurred in approximately one-third of participants in each group (low certainty evidence). A second multicenter, two-arm RCT conducted in India enrolled 374 participants older than 5 years of age with corneal abrasion who presented

within 48 hours after injury. This study investigated the effect of a three-day course of either ocular ointment combinations of chloramphenicol-clotrimazole or chloramphenicol-placebo (all three times daily). At day 3, 169 (100%) participants in the chloramphenicol-clotrimazole arm and 203 (99%) out of 205 participants in the chloramphenicol-placebo arm were cured without any complication, defined as complete epithelialization of the cornea without evidence of infection (RR 1.01, 95% CI 0.99 to 1.03; 374 participants; very low certainty evidence). Four participants assigned to the chloramphenicol-placebo arm experienced mild adverse events: two participants (1%) had mild chemosis and irritation, and two (1%) had small single sterile corneal infiltrates (low certainty evidence).
Authors' conclusions: Given the low to very low certainty of the available evidence, any beneficial effects of antibiotic prophylaxis in preventing ocular infection or accelerating epithelial healing following a corneal abrasion remain unclear. Moreover, the current evidence is insufficient to support any antibiotic regimen being superior to another. There is a need for a well-designed RCT assessing the efficacy and safety of ocular antibiotics in the treatment of corneal abrasion with a particular focus on high-risk populations and formulation of interventions.

Ophthalmology. 2022 Mar;129(3):322-333.
doi: 10.1016/j.ophtha.2021.10.016. Epub 2021 Oct 22.

Efficacy and Safety of 8 Atropine Concentrations for Myopia Control in Children: A Network Meta-Analysis

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Abstract
Topic: Comparative efficacy and safety of different concentrations of atropine for myopia control.
Clinical relevance: Atropine is known to be an effective intervention to delay myopia progression. Nonetheless, no well-supported evidence exists yet to rank the clinical outcomes of various concentrations of atropine.
Methods: We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov on April 14, 2021. We selected studies involving atropine treatment of at least 1 year's duration for myopia control in children. We performed a network meta-analysis (NMA) of randomized controlled trials (RCTs) and compared 8 atropine concentrations (1% to 0.01%). We ranked the atropine concentrations for the corresponding outcomes by P score (estimate of probability of being best treatment). Our primary outcomes were mean annual changes in refraction (diopters/year) and axial length (AXL; millimeters/year). We extracted data on the proportion of eyes showing myopia progression and safety outcomes (photopic and mesopic pupil diameter, accommodation amplitude, and distance and near best-corrected visual acuity [BCVA]).
Results: Thirty pairwise comparisons from 16 RCTs (3272 participants) were obtained. Our NMA ranked the 1%, 0.5%, and 0.05% atropine concentrations as the 3 most beneficial for myopia control, as assessed for both primary outcomes: 1% atropine (mean differences compared with control: refraction, 0.81 [95% confidence interval (CI), 0.58-1.04]; AXL, -0.35 [-0.46 to -0.25]); 0.5% atropine (mean differences compared with control: refraction, 0.70 [95% CI, 0.40-1.00]; AXL, -0.23 [-0.38 to -0.07]); 0.05% atropine (mean differences compared with

control: refraction, 0.62 [95% CI, 0.17-1.07]; AXL, -0.25 [-0.44 to -0.06]). In terms of myopia control as assessed by relative risk (RR) for overall myopia progression, 0.05% was ranked as the most beneficial concentration (RR, 0.39 [95% CI, 0.27-0.57]). The risk for adverse effects tended to rise as the atropine concentration was increased, although this tendency was not evident for distance BCVA. No valid network was formed for near BCVA.
Discussion: The ranking probability for efficacy was not proportional to dose (i.e., 0.05% atropine was comparable with that of high-dose atropine [1% and 0.5%]), although those for pupil size and accommodation amplitude were dose related.

Trachoma

Chin Med J (Engl). 2021 Sep 16;134(24):2944-2953.
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Effectiveness of azithromycin mass drug administration on trachoma: a systematic review
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Abstract
Backgrounds: Azithromycin mass drug administration (MDA) is a key part of the strategy for controlling trachoma. This systematic review aimed to comprehensively summarize the present studies of azithromycin MDA on trachoma; provide an overview of the impact of azithromycin MDA on trachoma in different districts; and explore the possible methods to enhance the effectiveness of azithromycin MDA in hyperendemic districts.
Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov were searched up to February 2021 with no language restriction. Studies reporting the effect of azithromycin MDA on trachoma were included. Mathematical modeling studies, animal studies, case reports, and reviews were excluded. The trachomatous inflammation-follicular (TF) <5.0% was used to judge the effect of azithromycin MDA on eliminating trachoma as a public health problem. Two researchers independently conducted the selection process and risk of bias assessment.
Results: A total of 1543 studies were screened, of which 67 studies including 13 cluster-randomized controlled trials and 54 non-randomized studies were included. The effect of azithromycin MDA on trachoma was closely related to the baseline prevalence in districts. For the districts with baseline prevalence between 5.0% and 9.9%, a single round of MDA achieved a TF <5.0%. For the districts with baseline between 10.0% and 29.9%, annual MDA for 3 to 5 years reduced TF <5.0%. However, for the districts with high level of baseline prevalence (TF >30.0%), especially with baseline TF >50.0%, annual MDA was unable to achieve the TF <5.0% even after 5 to 7 years of treatment. Quarterly MDA is more effective in controlling trachoma in these hyperendemic districts.
Conclusions: Azithromycin MDA for controlling trachoma depends on the baseline prevalence. The recommendation by the World Health Organization that annual MDA for 3 to 5 years in the districts with TF baseline >10.0% is not appropriate for all eligible districts.

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Stopping azithromycin mass drug administration for trachoma: A systematic review

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Abstract

The World Health Organization (WHO) recommends continuing azithromycin mass drug administration (MDA) for trachoma until endemic regions drop below 5% prevalence of active trachoma in children aged 1-9 years. Azithromycin targets the ocular strains of Chlamydia trachomatis that cause trachoma. Regions with low prevalence of active trachoma may have little if any ocular chlamydia, and, thus, may not benefit from azithromycin treatment. Understanding what happens to active trachoma and ocular chlamydia prevalence after stopping azithromycin MDA may improve future treatment decisions. We systematically reviewed published evidence for community prevalence of both active trachoma and ocular chlamydia after cessation of azithromycin distribution. We searched electronic databases for all peer-reviewed studies published before May 2020 that included at least 2 post-MDA surveillance surveys of ocular chlamydia and/or the active trachoma marker, trachomatous inflammation-follicular (TF) prevalence. We assessed trends in the prevalence of both indicators over time after stopping azithromycin MDA. Of 140 identified studies, 21 met inclusion criteria and were used for qualitative synthesis. Post-MDA, we found a gradual increase in ocular chlamydia infection prevalence over time, while TF prevalence generally gradually declined. Ocular chlamydia infection may be a better measurement tool compared to TF for detecting trachoma recrudescence in communities after stopping azithromycin MDA. These findings may guide future trachoma treatment and surveillance efforts.

Pain

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Efficacy and safety of pharmacological, physical, and psychological interventions for the management of chronic pain in children: a WHO systematic review and meta-analysis

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Abstract

Chronic pain in childhood is an international public health problem. We conducted a systematic review and meta-analysis to provide a summary of the published evidence of pharmacological, physical, and psychological therapies for children with chronic pain conditions. We searched CENTRAL, MEDLINE, EMBASE, and PsycINFO from inception to April

2020; clinical trial registries; and other sources for randomised controlled trials or comparative observational trials. We extracted critical outcomes of pain intensity, quality of life, physical functioning, role functioning, emotional functioning, sleep, and adverse events. We assessed studies for risk of bias and certainty of the evidence using GRADE. We included 34 pharmacological (4091 participants), 25 physical therapy (1470 participants), and 63 psychological trials (5025 participants). Participants reported a range of chronic pain conditions. Most studies were assessed to have unclear or high risk of bias across multiple domains. Pharmacological, physical, and psychological therapies showed some benefit for reducing pain, posttreatment, but only physical and psychological therapies improved physical functioning. We found no benefit of any treatment modality for health-related quality of life, role functioning, emotional functioning, or sleep. Adverse events were poorly reported, particularly for psychological and physical interventions. The largest evidence base for the management of chronic pain in children supports the use of psychological therapies, followed by pharmacological and physical therapies. However, we rated most outcomes as low or very low certainty, meaning further evidence is likely to change our confidence in the estimates of effects.

Research

BMC Med Res Methodol. 2021 Oct 17;21(1):212.
doi: 10.1186/s12874-021-01343-5.

Are morbidity and mortality estimates from randomized controlled trials externally valid? A comparison of outcomes among infants enrolled into an RCT or a cohort study in Botswana

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Abstract

Background: The external validity of the randomized controlled trial (RCT) refers to the extent to which the results of the RCT apply to the relevant, non-trial population and is impacted by its eligibility criteria, its organization, and its delivery of the intervention. Here, we compared the outcomes of mortality and hospitalization between an RCT and a cohort study that concurrently enrolled HIV-exposed uninfected (HEU) newborns in Botswana.

Methods: The Mpepu Study (the RCT) was a clinical trial which determined that co-trimoxazole (CTX) provided no survival benefit for HEUs, allowing both arms of the RCT to be used. The Maikaelelo study (the cohort study) was a prospective observational study that enrolled HEU newborns with telephone follow-up and no in-person visits. Rates of death and hospitalization in the pooled population, were modeled using cox-proportional hazards models for time to death or time to first hospitalization, with study setting (RCT vs. cohort study) as an independent variable. The causal effect of study setting on morbidity and mortality was obtained through a treatment effects approach.

Results: In total, 4,010 infants were included; 1,306 were enrolled into the cohort study and 2,704 were enrolled into the RCT. No significant differences in mortality were observed between the two study settings (HR: 1.28, 95% CI: 0.76, 2.13), but RCT participants had a lower risk of hospitalization (HR: 0.72, 95% CI: 0.58, 0.89) that decreased with age. However, RCT participants had a higher risk of hospitalization within the first six months of life. The

causal risk difference in hospitalizations attributable to the RCT setting was -0.03 (95% CI: -0.05, -0.01).
Conclusions: Children in an RCT with rigorous application of national standard of care guidelines experienced a significantly lower risk of hospitalization than children participating in a cohort study that did not alter clinical care. Future research is needed to further investigate outcome disparities when real-world results fail to mirror those achieved in a clinical trial.

School health and education

(See Adolescent health, Schistosomiasis)

Child Adolesc Psychiatry Ment Health. 2022 May 3;16(1):33.
doi: 10.1186/s13034-022-00470-1.
Effectiveness of a school-based mental health intervention for school teachers in urban Pakistan: a randomized controlled trial
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Abstract
Background: Schools have a major role in promoting children's physical and psychological health and well-being and the mental health literacy of all key stakeholders, especially teachers, is critical to achieving this goal. Teachers' knowledge and beliefs about psychological problems influence the way they deal with their students' mental health issues. This study is a preliminary investigation evaluating the effectiveness and feasibility of a School Mental Health Programme (SMHP) developed by the World Health Organization's Eastern Mediterranean Regional Office (WHO-EMRO) in improving mental health literacy and self-efficacy among school teachers in an inner-city area of urban Lahore.
Methods: Teachers were randomly assigned to 3 days standardized WHO-EMRO School Mental Health Manual based Intervention (n = 118) or to a wait list delayed intervention control group (n = 113). Teachers were assessed pre and post training and at 3 months follow up using measures for mental health literacy (Primary outcome) and self-efficacy. School Heads completed the WHO School Psychosocial Profile and students reported socioemotional skills and psychological problems using Strengths and Difficulties questionnaire at baseline and 3 months post intervention.
Results: Compared with waitlist group, teachers in intervention group presented a significant increase in mental health literacy ($F_{2,181}$ = 8.92; P < 0.001), as well as better teacher's self-efficacy in classroom management and student engagement ($F_{2,181}$ = 16.45; P ≤ 0.000 and $F_{2,181}$ = 4.65; P ≤ 0.011, respectively). Increase confidence in helping students with mental health problems was also noted in the intervention arm ($F_{2,181}$ = 15.96 P ≤ 0.000). Improvement in overall school environment was also found. No statistical difference in the emotional and behavioural difficulties in students was noticed at 3 months.
Conclusion: This study is one of the first preliminary investigation of WHO-EMRO school mental health intervention in Pakistan. The study showed that intervention led to significant improvement in mental health literacy and self-efficacy among teachers, which was largely sustained over time. Despite a major limitation of lack of clustering and likely contamination affecting follow up outcomes, the study showed promising results in the context of mental

health promotion, prevention and early intervention in schools in Lahore, Pakistan. A larger cluster randomised trial is justified, given the level of participant engagement and acceptability by schools.

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School-Based Nutrition Interventions in Children Aged 6 to 18 Years: An Umbrella Review of Systematic Reviews

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Abstract

Schools are identified as a key setting to influence children's and adolescents' healthy eating. This umbrella review synthesised evidence from systematic reviews of school-based nutrition interventions designed to improve dietary intake outcomes in children aged 6 to 18 years. We undertook a systematic search of six electronic databases and grey literature to identify relevant reviews of randomized controlled trials. The review findings were categorised for synthesis by intervention type according to the World Health Organisation Health Promoting Schools (HPS) framework domains: nutrition education; food environment; all three HPS framework domains; or other (not aligned to HPS framework domain). Thirteen systematic reviews were included. Overall, the findings suggest that school-based nutrition interventions, including nutrition education, food environment, those based on all three domains of the HPS framework, and eHealth interventions, can have a positive effect on some dietary outcomes, including fruit, fruit and vegetables combined, and fat intake. These results should be interpreted with caution, however, as the quality of the reviews was poor. Though these results support continued public health investment in school-based nutrition interventions to improve child dietary intake, the limitations of this umbrella review also highlight the need for a comprehensive and high quality systematic review of primary studies.

Surgical problems

Am J Obstet Gynecol MFM. 2022 Jul;4(4):100651.
doi: 10.1016/j.ajogmf.2022.100651. Epub 2022 Apr 22.

Preterm vs term delivery in antenatally diagnosed gastroschisis: a systematic review and meta-analysis

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Abstract

Objective: To review the evidence regarding gestational age at birth, length of stay, sepsis incidence, days on mechanical ventilation, and mortality between preterm and term deliveries in pregnancies complicated by gastroschisis.

Data sources: We conducted database searches of PubMed, Cochrane Central Register of Controlled Trials, Embase, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov without language restrictions through August 16, 2021. References of all relevant articles were reviewed.
Study eligibility criteria: Randomized controlled trials, nonrandomized controlled trials, and observational studies were evaluated comparing length of stay, sepsis, days on mechanical ventilation, and mortality between either elective preterm delivery and expectant management (Group 1) or preterm gestational age and term gestational age (Group 2).
Methods: Two researchers independently selected studies and evaluated risk of bias with the Risk of Bias 2 tool for randomized controlled trials and the Newcastle-Ottawa Scale for cohort studies. Mean differences and odds ratios were calculated using a random-effects model for inclusion and methodological quality. The primary outcome was length of stay. Secondary outcomes were incidence of sepsis, mortality, days on mechanical ventilation, and gestational age.
Results: Thirty studies with a total of 7409 patients were included in the systematic review, of which 25 were included in the analysis. Group 1 studies found no difference in length of stay or mortality and a trend toward fewer days on mechanical ventilation (mean difference, -0.40; 95% confidence interval, -0.89 to -0.10; P=.12; I^2=35%). Subgroup analysis excluding premature delivery demonstrated lower sepsis incidence in elective preterm delivery (odds ratio, 0.46; 95% confidence interval, 0.25-0.84; P=.01; I^2=0%). Group 2 studies found increased length of stay (mean difference, 15.44; 95% confidence interval, 8.44-21.83; P<.00001; I^2=94%), sepsis (odds ratio, 1.69; 95% confidence interval, 1.15-2.50; P=.008; I^2=51%), days on mechanical ventilation (mean difference, 1.38; 95% confidence interval, 0.10-2.66; P=.03; I^2=66%), and mortality (odds ratio, 2.97; 95% confidence interval, 1.59-5.55; P=.0007; I^2=0%). Gestational age was significantly lower in Group 2 studies than in Group 1 studies.
Conclusion: Data continue to be conflicting, but subgroup analysis suggested a possible reduction in sepsis incidence and mean days on mechanical ventilation with elective early term delivery.

Cochrane Database Syst Rev. 2022 Apr 26;4(4):CD013714.
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Probiotics for the prevention of Hirschsprung-associated enterocolitis

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Abstract
Background: Hirschsprung-associated enterocolitis (HAEC) is a leading cause of serious morbidity and potential mortality in children with Hirschsprung's disease (HD). People with HAEC suffer from intestinal inflammation, and present with diarrhoea, explosive stools, and abdominal distension. Probiotics are live microorganisms with beneficial health effects, which can optimise gastrointestinal function and gut flora. However, the efficacy and safety of probiotic supplementation in the prevention of HAEC remains unclear.
Objectives: To assess the effects of probiotic supplements used either alone or in combination with pharmacological interventions on the prevention of Hirschsprung-associated enterocolitis.

Search methods: We searched CENTRAL, PubMed, Embase, the China BioMedical Literature database (CBM), the World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, the Chinese Clinical Trials Registry, Australian New Zealand Clinical Trials Registry, and Clinical Trials Registry-India, from database inception to 27 February 2022. We also searched the reference lists of relevant articles and reviews for any additional trails.
Selection criteria: Randomised controlled trials (RCTs) comparing probiotics and placebo, or any other non-probiotic intervention, for the prevention of HAEC were eligible for inclusion.
Data collection and analysis: Two review authors independently extracted data and assessed the risk of bias of the included studies; disagreements were resolved by discussion with a third review author. We assessed the certainty of evidence using the GRADE approach. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes.
Main results: We included two RCTs, with a total of 122 participants. We judged the overall risk of bias as high. We downgraded the evidence due to risk of bias (random sequence generation, allocation concealment, and blinding) and small sample size. The evidence is very uncertain about the effect of probiotics on the occurrence of HAEC (OR 0.58, 95% CI 0.10 to 3.43; I^2 = 74%; 2 studies, 120 participants; very low-certainty evidence). We found one included study that did not measure serious adverse events and one included study that reported no serious adverse events related to probiotics. Probiotics may result in little to no difference between probiotics and placebo in relation to the severity of children with HAEC at Grade I (OR 0.66, 95% CI 0.14 to 3.16; I^2 = 25%; 2 studies, 120 participants; low-certainty evidence). The effects of probiotics on the severity of HAEC at Grade II are very uncertain (OR 1.14, 95% CI 0.01 to 136.58; I^2 = 86%; 2 studies, 120 participants; very low-certainty evidence). Similarly, the evidence suggests that probiotics results in little to no difference in relation to the severity of HAEC at Grade III (OR 0.43, 95% CI 0.05 to 3.45; I^2 = 0%; 2 studies, 120 participants; low-certainty evidence). No overall mortality or withdrawals due to adverse events were reported. Probiotics may result in little to no difference in the recurrence of episodes of HAEC compared to placebo (OR 0.85, 95% CI 0.24 to 3.00; 1 study, 60 participants; low-certainty evidence).
Authors' conclusions: There is currently not enough evidence to assess the efficacy or safety of probiotics for the prevention of Hirschsprung-associated enterocolitis when compared with placebo. The presence of low- to very-low certainty evidence suggests that further well-designed and sufficiently powered RCTs are needed to clarify the true efficacy of probiotics.

Trypanosomiasis

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Chemotherapy for second-stage human African trypanosomiasis: drugs in use
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Abstract

Background: Human African trypanosomiasis, or sleeping sickness, is a severe disease affecting people in the poorest parts of Africa. It is usually fatal without treatment. Conventional treatments require days of intravenous infusion, but a recently developed drug, fexinidazole, can be given orally. Another oral drug candidate, acoziborole, is undergoing clinical development and will be considered in subsequent editions.
OBJECTIVES: To evaluate the effectiveness and safety of currently used drugs for treating second-stage Trypanosoma brucei gambiense trypanosomiasis (gambiense human African trypanosomiasis, g-HAT).
Search methods: On 14 May 2021, we searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Latin American and Caribbean Health Science Information database, BIOSIS, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. We also searched reference lists of included studies, contacted researchers working in the field, and contacted relevant organizations.
Selection criteria: Eligible studies were randomized controlled trials that included adults and children with second-stage g-HAT, treated with anti-trypanosomal drugs currently in use.
Data collection and analysis: Two review authors extracted data and assessed risk of bias; a third review author acted as an arbitrator if needed. The included trial only reported dichotomous outcomes, which we presented as risk ratio (RR) or risk difference (RD) with 95% confidence intervals (CI). MAIN RESULTS: We included one trial comparing fexinidazole to nifurtimox combined with eflornithine (NECT). This trial was conducted between October 2012 and November 2016 in the Democratic Republic of the Congo and the Central African Republic, and included 394 participants. The study reported on efficacy and safety, with up to 24 months' follow-up. We judged the study to be at low risk of bias in all domains except blinding; as the route of administration and dosing regimens differed between treatment groups, participants and personnel were not blinded, resulting in a high risk of performance bias. Mortality with fexinidazole may be higher at 24 months compared to NECT. There were 9/264 deaths in the fexinidazole group and 2/130 deaths in the NECT group (RR 2.22, 95% CI 0.49 to 10.11; 394 participants; low-certainty evidence). None of the deaths were related to treatment. Fexinidazole likely results in an increase in the number of people relapsing during follow-up, with 14 participants in the fexinidazole group (14/264) and none in the NECT group (0/130) relapsing at 24 months (RD 0.05, 95% CI 0.02 to 0.08; 394 participants; moderate-certainty evidence). We are uncertain whether there is any difference between the drugs regarding the incidence of serious adverse events at 24 months. (31/264 with fexinidazole and 13/130 with NECT group at 24 months). Adverse events were common with both drugs (247/264 with fexinidazole versus 121/130 with NECT), with no difference between groups (RR 1.01, 95% CI 0.95 to 1.06; 394 participants; moderate-certainty evidence). AUTHORS' CONCLUSIONS: Oral treatment with fexinidazole is much easier to administer than conventional treatment, but deaths and relapse appear to be more common. However, the advantages or an oral option are considerable, in terms of convenience, avoiding hospitalisation and multiple intravenous infusions, thus increasing adherence.

Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

Lancet Infect Dis. 2022 Apr;22(4):507-518.
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Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis

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Abstract

Background: The WHO-recommended tuberculosis screening and diagnostic algorithm in ambulatory people living with HIV is a four-symptom screen (known as the WHO-recommended four symptom screen [W4SS]) followed by a WHO-recommended molecular rapid diagnostic test (eg Xpert MTB/RIF [hereafter referred to as Xpert]) if W4SS is positive. To inform updated WHO guidelines, we aimed to assess the diagnostic accuracy of alternative screening tests and strategies for tuberculosis in this population.

Methods: In this systematic review and individual participant data meta-analysis, we updated a search of PubMed (MEDLINE), Embase, the Cochrane Library, and conference abstracts for publications from Jan 1, 2011, to March 12, 2018, done in a previous systematic review to include the period up to Aug 2, 2019. We screened the reference lists of identified pieces and contacted experts in the field. We included prospective cross-sectional, observational studies and randomised trials among adult and adolescent (age ≥10 years) ambulatory people living with HIV, irrespective of signs and symptoms of tuberculosis. We extracted study-level data using a standardised data extraction form, and we requested individual participant data from study authors. We aimed to compare the W4SS with alternative screening tests and strategies and the WHO-recommended algorithm (ie, W4SS followed by Xpert) with Xpert for all in terms of diagnostic accuracy (sensitivity and specificity), overall and in key subgroups (eg, by antiretroviral therapy [ART] status). The reference standard was culture. This study is registered with PROSPERO, CRD42020155895.

Findings: We identified 25 studies, and obtained data from 22 studies (including 15 666 participants; 4347 [27·7%] of 15 663 participants with data were on ART). W4SS sensitivity was 82% (95% CI 72-89) and specificity was 42% (29-57). C-reactive protein (≥10 mg/L) had

similar sensitivity to (77% [61-88]), but higher specificity (74% [61-83]; n=3571) than, W4SS. Cough (lasting ≥2 weeks), haemoglobin (<10 g/dL), body-mass index (<18·5 kg/m^2), and lymphadenopathy had high specificities (80-90%) but low sensitivities (29-43%). The WHO-recommended algorithm had a sensitivity of 58% (50-66) and a specificity of 99% (98-100); Xpert for all had a sensitivity of 68% (57-76) and a specificity of 99% (98-99). In the one study that assessed both, the sensitivity of sputum Xpert Ultra was higher than sputum Xpert (73% [62-81] vs 57% [47-67]) and specificities were similar (98% [96-98] vs 99% [98-100]). Among outpatients on ART (4309 [99·1%] of 4347 people on ART), W4SS sensitivity was 53% (35-71) and specificity was 71% (51-85). In this population, a parallel strategy (two tests done at the same time) of W4SS with any chest x-ray abnormality had higher sensitivity (89% [70-97]) and lower specificity (33% [17-54]; n=2670) than W4SS alone; at a tuberculosis prevalence of 5%, this strategy would require 379 more rapid diagnostic tests per 1000 people living with HIV than W4SS but detect 18 more tuberculosis cases. Among outpatients not on ART (11 160 [71·8%] of 15 541 outpatients), W4SS sensitivity was 85% (76-91) and specificity was 37% (25-51). C-reactive protein (≥10 mg/L) alone had a similar sensitivity to (83% [79-86]), but higher specificity (67% [60-73]; n=3187) than, W4SS and a sequential strategy (both test positive) of W4SS then C-reactive protein (≥5 mg/L) had a similar sensitivity to (84% [75-90]), but higher specificity than (64% [57-71]; n=3187), W4SS alone; at 10% tuberculosis prevalence, these strategies would require 272 and 244 fewer rapid diagnostic tests per 1000 people living with HIV than W4SS but miss two and one more tuberculosis cases, respectively.
Interpretation: C-reactive protein reduces the need for further rapid diagnostic tests without compromising sensitivity and has been included in the updated WHO tuberculosis screening guidelines. However, C-reactive protein data were scarce for outpatients on ART, necessitating future research regarding the utility of C-reactive protein in this group. Chest x-ray can be useful in outpatients on ART when combined with W4SS. The WHO-recommended algorithm has suboptimal sensitivity; Xpert for all offers slight sensitivity gains and would have major resource implications.

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Randomized Clinical Trial of High Dose Rifampicin with or without Levofloxacin versus Standard of Care for Paediatric Tuberculous Meningitis: The TBM-KIDS Trial

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Abstract

Background: Pediatric tuberculous meningitis (TBM) commonly causes death or disability. . In adults, high-dose rifampicin may reduce mortality. Fluoroquinolones' role remains unclear. There have been no antimicrobial treatment trials for pediatric TBM.
Methods: TBM-KIDS (NCT02958709) was a Phase II open-label randomized trial among children with TBM in India and Malawi. Participants received isoniazid and pyrazinamide plus: (a) high-dose rifampicin (30 mg/kg) and ethambutol (R30HZE, Arm 1); (b) high-dose

rifampicin and levofloxacin (R30HZL, Arm 2); or (c) standard-dose rifampicin and ethambutol (R15HZE, Arm 3) for 8 weeks, followed by 10 months of standard treatment. Functional and neurocognitive outcomes were measured longitudinally using Modified Rankin Scale (MRS) and Mullen Scales of Early Learning (MSEL).
Results: Of 2487 children pre-screened, 79 were screened, and 37 enrolled. Median age was 72 months. 49%, 43%, and 8% had Stage I, II, and III disease. Grade 3 or higher adverse events occurred in 58%, 55%, and 36% of children in Arms 1, 2, and 3, with one death (Arm 1) and six early treatment discontinuations (4 in Arm 1, 1 each in Arms 2 and 3). By Week 8, all children recovered to MRS score of 0 or 1. Average MSEL scores were significantly better in Arm 1 than Arm 3 in fine motor, receptive language, and expressive language domains ($p<0.01$).
Conclusions: In a pediatric TBM trial, functional outcomes were excellent overall. The trend towards higher frequency of adverse events but better neurocognitive outcomes in children receiving high-dose rifampicin requires confirmation in a larger trial.

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Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children
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Abstract
Background: Two thirds of children with tuberculosis have nonsevere disease, which may be treatable with a shorter regimen than the current 6-month regimen.
Methods: We conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 months (16 weeks) or 6 months (24 weeks) of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the World Health Organization. The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified intention-to-treat population). A noninferiority margin of 6 percentage points was used. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment.
Results: From July 2016 through July 2018, a total of 1204 children underwent randomization (602 in each group). The median age of the participants was 3.5 years (range, 2 months to 15 years), 52% were male, 11% had human immunodeficiency virus infection, and 14% had bacteriologically confirmed tuberculosis. Retention by 72 weeks was 95%, and adherence to the assigned treatment was 94%. A total of 16 participants (3%) in the 4-month

group had a primary-outcome event, as compared with 18 (3%) in the 6-month group (adjusted difference, -0.4 percentage points; 95% confidence interval, -2.2 to 1.5). The noninferiority of 4 months of treatment was consistent across the intention-to-treat, per-protocol, and key secondary analyses, including when the analysis was restricted to the 958 participants (80%) independently adjudicated to have tuberculosis at baseline. A total of 95 participants (8%) had an adverse event of grade 3 or higher, including 15 adverse drug reactions (11 hepatic events, all but 2 of which occurred within the first 8 weeks, when the treatments were the same in the two groups).
Conclusions: Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, nonsevere, smear-negative tuberculosis. (Funded by the U.K. Medical Research Council and others; SHINE ISRCTN number, ISRCTN63579542.).

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Completion of isoniazid-rifapentine (3HP) for tuberculosis prevention among people living with HIV: Interim analysis of a hybrid type 3 effectiveness-implementation randomized trial

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Abstract
Background: Scaling up shorter regimens for tuberculosis (TB) prevention such as once weekly isoniazid-rifapentine (3HP) taken for 3 months is a key priority for achieving targets set forth in the World Health Organization's (WHO) END TB Strategy. However, there are few data on 3HP patient acceptance and completion in the context of routine HIV care in sub-Saharan Africa.
Methods and findings: The 3HP Options Trial is a pragmatic, parallel type 3 effectiveness-implementation randomized trial comparing 3 optimized strategies for delivering 3HP-facilitated directly observed therapy (DOT), facilitated self-administered therapy (SAT), or informed choice between DOT and SAT using a shared decision-making aid-to people receiving care at a large urban HIV clinic in Kampala, Uganda. Participants and healthcare providers were not blinded to arm assignment due to the nature of the 3HP delivery strategies. We conducted an interim analysis of participants who were enrolled and exited the 3HP treatment period between July 13, 2020 and April 30, 2021. The primary outcome, which was aggregated across trial arms for this interim analysis, was the proportion who accepted and completed 3HP (≥11 of 12 doses within 16 weeks of randomization). We used Bayesian inference analysis to estimate the posterior probability that this proportion would exceed 80% under at least 1 of the 3HP delivery strategies, a coprimary hypothesis of the trial. Through April 2021, 684 participants have been enrolled, and 479 (70%) have exited the treatment period. Of these 479 participants, 309 (65%) were women, mean age was 41.9 years (standard deviation (SD): 9.2), and mean time on antiretroviral therapy (ART) was 7.8 years (SD: 4.3). In total, 445 of them (92.9%, 95% confidence interval (CI): [90.2 to 94.9])

accepted and completed 3HP treatment. There were no differences in treatment acceptance and completion by sex, age, or time on ART. Treatment was discontinued due to a documented adverse event (AE) in 8 (1.7%) patients. The probability that treatment acceptance and completion exceeds 80% under at least 1 of the three 3HP delivery strategies was greater than 99%. The main limitations are that the trial was conducted at a single site, and the interim analysis focused on aggregate outcome data to maintain blinding of investigators to arm-specific outcomes.
Conclusions: 3HP was widely accepted by people living with HIV (PLHIV) in Uganda, and very high levels of treatment completion were achieved in a programmatic setting. These findings show that 3HP can enable effective scale-up of tuberculosis preventive therapy (TPT) in high-burden countries, particularly when delivery strategies are tailored to target known barriers to treatment completion.

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The diagnostic performance of novel skin-based in-vivo tests for tuberculosis infection compared with purified protein derivative tuberculin skin tests and blood-based in vitro interferon-γ release assays: a systematic review and meta-analysis

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Abstract
Background: Novel skin-based tests for tuberculosis infection might present suitable alternatives to current tests; however, diagnostic performance of new tests compared with the purified protein derivative-tuberculin skin test (TST) or interferon-γ release assays (IGRA) needs systematic assessment.
Methods: In this systematic review and meta-analysis, we searched English (Medline OVID), Chinese (Chinese Biomedical Literature Database and the China National Knowledge Infrastructure), and Russian (e-library) databases from the inception of each database to May 15, 2019, (with updated search of the Russian and English databases on Oct, 20 2020) using terms "ESAT6" OR "CFP10" AND "skin test" AND "Tuberculosis" OR "C-Tb" OR "Diaskintest". We included studies reporting on the performance of index tests alone or compared with a comparator. Inclusion criteria varied according to review objectives and performance outcome, but reporting of test cut-offs for positivity applied to study population was required from all studies. We used a hierarchy of reference standards for tuberculosis infection consistent with the 2020 WHO framework to evaluate diagnostic performance. Two authors independently reviewed the titles and abstracts for English and Chinese (LF and MK) and Russian studies (MK and VN). Study quality was assessed with QUADAS-2. Pooled random-effects estimates are presented when appropriate for total agreement proportion, sensitivity in microbiologically confirmed tuberculosis and specificity in cohorts with low risk of tuberculosis infection. This study is registered with PROSPERO, CRD42019135572.
Findings: We identified 1466 original articles, of which 37 (2·5%) studies, including 10 915 individuals (7111 Diaskintest, 2744 C-Tb, 887 EC, 173 DPPD), were included in the qualitative analysis (29 [78%] studies of Diaskintest, five [15%] studies of C-Tb, two [5%] studies of EC-skintest, and one [3%] study of DPPD). 22 (1·5%) studies including 5810 individuals (3143

Diaskintest, 2129 C-Tb, 538 EC-skintest) were included in the quantitative analysis: 15 (68%) of Diaskintest, five (23%) of C-Tb, and two (9%) of EC-skintest. Tested sub-populations included individuals with HIV, children (0-18 years), and individuals exposed to tuberculosis. Studies were heterogeneous with moderate to high risk of bias. Nine head-to-head studies of index test versus TST and IGRA permitted direct comparisons and pooling. In a mixed cohort of people with and without tuberculosis, Diaskintest pooled agreement with IGRA was 87·16% (95% CI 79·47-92·24) and 55·45% (46·08-64·45) with TST-5 mm cut-off ($TST^{5\ mm}$). Diaskintest sensitivity was 91·18% (95% CI 81·72-95·98) compared with 88·24% (78·20-94·01) for $TST^{5\ mm}$, 89·66 (78·83-95·28) for IGRA QuantiFERON, and 90·91% (79·95-96·16) for TSPOT.TB. C-Tb agreement with IGRA in individuals with active tuberculosis was 79·80% (95% CI 76·10-83·07) compared with 78·92% (74·65-82·63) for TST5 mm/15 mm cut-off ($TST^{5\ mm/15\ mm}$). $TST^{5/15mm}$ reflects threshold in cohorts that applied stratified cutoffs: 5 mm for HIV-infected, immunocompromised, or BCG-naive individuals, and 15mm for BCG-vaccinated immunocompetent individuals. C-Tb sensitivity was 74·52% (95% CI 70·39-78·25) compared with a sensitivity of 78·18% (67·75-85·94) for $TST^{5\ mm/15\ mm}$, and 71·67% (63·44-78·68) for IGRA. Specificity was 97·85% (95% CI 93·96-99·25) for C-Tb versus 93·31% (90·22-95·48) for TST 15 mm cut-off and 99·15% (79·66-99·97) for IGRA. EC-skintest sensitivity was 86·06% (95% CI 82·39-89·07).

Interpretation: Novel skin-based tests for tuberculosis infection appear to perform similarly to IGRA or TST; however, study quality varied. Evaluation of test performance, patient-important outcomes, and diagnostic use in current clinical algorithms will inform implementation in key populations.

Ultasound

Pediatrics. 2022 May 1;149(5):e2021055523.
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Ultrasound for Pediatric Peripheral Intravenous Catheter Insertion: A Systematic Review

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Abstract

Background and objectives: Establishing peripheral intravenous catheter (PIVC) access in infants and children is a common procedure but can be technically difficult. The primary objective was to determine the effect ultrasound had on first attempt PIVC insertion success rates in the pediatric population. Secondary objectives included overall success rates and subgroups analyses.

Methods: A systematic review of articles using Medline, Embase, CENTRAL, World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov. Randomized trials evaluating ultrasound-guided PIVC insertion against the landmark approach in pediatric patients who reported at least 1 outcome of success rate (first attempt or overall) were included. Methodological quality of the literature was assessed using the Revised Cochrane risk-of-bias tool for randomized trials. A meta-analysis using a random-effects model was performed.

Results: Nine studies with 1350 patients, from a total of 1033 studies, were included for analysis. Ultrasound showed a statistically significant improvement in PIVC insertion success on first attempt in 5 of 8 studies, with an overall success rate of 78% in the ultrasound group and 66% in the control group. The secondary outcome of overall success was improved by ultrasound in studies that allowed ≥3 attempts (pooled OR 3.57, 95% CI 2.05 to 6.21, P < .001, I2 = 0.0%).
Conclusions: This systematic review suggested that ultrasound improves pediatric PIVC first pass and overall success rates. Subgroup analysis showed improvement in PIVC success rates for patients with difficult intravenous access and a single operator, dynamic, short-axis ultrasound technique.

Vaccines and immunization

(see also deworming)

Cholera vaccine

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doi: 10.1016/j.vaccine.2021.06.069. Epub 2021 Jul 1.

A phase I/II study to evaluate safety, tolerability and immunogenicity of Hillchol®, an inactivated single Hikojima strain based oral cholera vaccine, in a sequentially age descending population in Bangladesh

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Abstract
Background: The World Health Organization (WHO) recommends the use of oral cholera vaccines (OCVs) as part of an integrated control program, both in highly endemic settings and during cholera epidemics. The available and internationally recommended WHO-prequalified OCVs (Dukoral, Shanchol, Euvichol) contain multiple heat and formalin-killed V. cholerae strains of Inaba and Ogawa serotypes. MSD Wellcome Trust Hilleman Laboratories Pvt. Ltd. in technical collaboration with University of Gothenburg, Sweden has developed a new single strain OCV, Hillchol. This vaccine consists of formaldehyde-inactivated whole cell El Tor V. cholerae O1 bacteria engineered into the Hikojima serotype for stable expression of both the Ogawa (AB) and Inaba (AC) LPS antigens on the bacterial surface. We evaluated the safety and immunogenicity of this novel and potentially much less expensive OCV in comparison with Shanchol.
Methods: We conducted a randomized, non-inferiority, age-descending clinical trial of OCV (Hillchol vs. Shanchol) in the Mirpur area of Dhaka city from July 2016 to May 2017. This study was carried out in three different age cohorts (1-<5, 5-17 and ≥18 years old). Two doses of vaccine were given at 14 days intervals to 560 healthy participants.
Findings: No serious adverse events were reported. There were no significant differences in the rates of adverse events between the test vaccine (Hillchol) and the comparator (Shanchol) group. Serum vibriocidal antibody responses in all age groups combined were

comparable for all the O1 Ogawa (59% vs. 67%; 90% CI of difference: -14.55, -0.84) and Inaba (70% vs. 71%; 90% CI of difference: -7.24, 5.77) serotypes, showing that the Hillchol vaccine was non-inferior to Shanchol. This new vaccine was also non-inferior to Shanchol in the different age strata.
Conclusion: The safety and immunogenicity profile of the new OCV Hillchol is comparable to Shanchol in persons residing in a cholera-endemic setting

Enterovirus 71 vaccine

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Immunogenicity and safety of inactivated enterovirus A71 vaccines in children aged 6-35 months in China: a non-inferiority, randomised controlled trial
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Abstract
Background: China's three inactivated enterovirus A71 (EV-A71) vaccines are the first and currently world's only EV-A71 vaccines approved by a national regulatory authority and used to prevent EV-A71 associated diseases. The three vaccines vary by vaccine strain, manufacturing cell substrate, and antigen dose, but no head-to-head comparisons of these vaccines have been done. We compared immunogenicity of the vaccines in children 6-35 months old.
Methods: We recruited healthy children aged 6-35 months who lived in a study site county into a multicentre, open-label, non-inferiority, three-group, randomised controlled trial that was conducted in five counties in China. Enrolled children were randomly assigned (1:1:1) to receive two doses of one of the three EV-A71 vaccines. The primary outcome was the proportion of children with EV-A71 neutralizing antibody seroconversion 4 weeks after the second dose; a secondary outcome was adverse events in the 4 weeks after each dose. Analyses of immunogenicity included all children who completed the study (per-protocol analysis). Safety analysis included all children completed safety follow-up after at least one. We used a 10% margin to establish non-inferiority. This trial was registered on a World Health Organization platform: Chinese Clinical Trial Registry (ChiCTR1900026663).
Findings: 1631 children were assessed for eligibility between Nov 4 and Nov 20, 2019. Of 1500 (92%) enrolled children, 500 were assigned to vaccine group A, B, or C; 483 in group A,484 in group B, and 487 in group C completed the study. Before dose one, the seropositive rates in groups A, B, and C were 9.7%, 7.2%, and 7.0%. Four weeks after the second dose, seroconversion rates of groups A, B, and C were 98.8%, 99.4% and 99.8% - mutually non-inferior in all two-group comparisons. There were no serious adverse events in any group and no evidence of a difference among the three groups in the incidence of local adverse event or systemic adverse event. Fever was the most common adverse event. All children with reported adverse events recovered.
Interpretation: Non-inferior and high seroconversion rates and equivalent safety of three EV-A71 vaccines supports use any of these vaccines to prevent EV-A71-associated diseases.

These results may be useful for regulators, vaccine policy makers, and immunization programmes in China and in countries where EV-A71 is endemic.

Malaria vaccine

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Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention

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Abstract

Background: Malaria control remains a challenge in many parts of the Sahel and sub-Sahel regions of Africa.

Methods: We conducted an individually randomized, controlled trial to assess whether seasonal vaccination with RTS,S/AS01$_E$ was noninferior to chemoprevention in preventing uncomplicated malaria and whether the two interventions combined were superior to either one alone in preventing uncomplicated malaria and severe malaria-related outcomes.

Results: We randomly assigned 6861 children 5 to 17 months of age to receive sulfadoxine-pyrimethamine and amodiaquine (2287 children [chemoprevention-alone group]), RTS,S/AS01$_E$ (2288 children [vaccine-alone group]), or chemoprevention and RTS,S/AS01$_E$ (2286 children [combination group]). Of these, 1965, 1988, and 1967 children in the three groups, respectively, received the first dose of the assigned intervention and were followed for 3 years. Febrile seizure developed in 5 children the day after receipt of the vaccine, but the children recovered and had no sequelae. There were 305 events of uncomplicated clinical malaria per 1000 person-years at risk in the chemoprevention-alone group, 278 events per 1000 person-years in the vaccine-alone group, and 113 events per 1000 person-years in the combination group. The hazard ratio for the protective efficacy of RTS,S/AS01$_E$ as compared with chemoprevention was 0.92 (95% confidence interval [CI], 0.84 to 1.01), which excluded the prespecified noninferiority margin of 1.20. The protective efficacy of the combination as compared with chemoprevention alone was 62.8% (95% CI, 58.4 to 66.8) against clinical malaria, 70.5% (95% CI, 41.9 to 85.0) against hospital admission with severe malaria according to the World Health Organization definition, and 72.9% (95% CI, 2.9 to 92.4) against death from malaria. The protective efficacy of the combination as compared with the vaccine alone against these outcomes was 59.6% (95% CI, 54.7 to 64.0), 70.6% (95% CI, 42.3 to 85.0), and 75.3% (95% CI, 12.5 to 93.0), respectively.

Conclusions: Administration of RTS,S/AS01$_E$ was noninferior to chemoprevention in preventing uncomplicated malaria. The combination of these interventions resulted in a substantially lower incidence of uncomplicated malaria, severe malaria, and death from malaria than either intervention alone.

Prentavalent vaccine (DTP-HepB-Hib)

Indian Pediatr. 2021 Dec 15;58(12):1131-1135.
Immunogenicity and Safety of Three WHO Prequalified (DTwP -HB-Hib) Pentavalent Combination Vaccines Administered As Per Iranian National Immunization Plan in Iranian Infants: A Randomized, Phase III Study
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Free article
Abstract
Background: The pentavalent vaccine Pentavac was officially introduced in the Iranian National Immunization Plan in November, 2014.
Objective: To compare the immunogenicity and safety of Pentavac vaccine (Serum Institute of India Ltd.) with two other pentavalent vaccines available in Iran, i.e., Pentabio (PT Bio Farma (Persero)) and Shan 5 (Shantha Biotechnics Ltd.).
Design: Randomized, phase III study.
Participants: 900 infants attending the study sites to receive the vaccine at 2, 4, and 6 months of age.
Intervention: Infants were randomly assigned to one of the Pentavac, Pentabio, and Shan 5 vaccine groups.
Outcomes: The antibody titers were measured against five antigens, diphtheria, tetanus, pertussis, Haemophilus influenzae B, and hepatitis B before receiving the first dose and one month after the last dose. The adverse events following vaccination after each dose were recorded in the adverse events diary.
Results: All vaccines showed similar immunogenicity against four of the five antigens except pertussis. While vaccination with Shan 5 resulted in the highest immunogenicity against pertussis, Pentabio was significantly lower than the other two vaccines (P<0.001). The incidence of local adverse events significantly differed among the three vaccine brands (P<0.001), but the incidence of most of the evaluated systemic adverse events was similar (P>0.05).
Conclusions: Pentavac and Shan 5 had similar immunogenicity, the former having better immunogenicity against pertussis than Pentabio. Pentavac and Pentabio had a comparable safety profile.

Rabies vaccine

Int J Infect Dis. 2021 Nov;112:89-95.
doi: 10.1016/j.ijid.2021.09.025. Epub 2021 Sep 20.
Immunogenicity of 2-dose pre-exposure rabies vaccine co-administered with quadrivalent influenza vaccine in children
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Abstract

Objectives: The World Health Organization recommends a 2-dose rabies pre-exposure prophylaxis (PrEP) regimen. This study aimed to compare the immunogenicity of rabies PrEP regimens co-administered with inactivated quadrivalent influenza vaccine (IIV4).
Methods: Children aged 3 to 9 years were randomly assigned (2:2:1) to receive 0.25 mL of chromatographically purified Vero cell rabies vaccine intramuscularly: Group A at day 0, 7 with IIV4; Group B at day 0, 28 with IIV4; Group C at day 0, 7. A booster-dose of CPRV was given on day 365. Primary outcome was the proportion of children with protective rabies virus neutralizing antibody (RVNA) ≥ 0.5 IU/mL, on day 42 and 7 days post-booster.
Results: From November 2019 to January 2020; 100 children with a median age (IQR) of 5.4 years (4.8-7.3) were enrolled. All participants achieved protective RVNA titers on day 42 and 7-days post booster. Geometric mean titers (GMT) at day 42 were Group A, 8.98(95%CI 7.06-11.42); Group B, 23.89(95%CI 19.33-29.51); Group C, 9.94(95%CI 7.03-14.06). Likewise, RVNA GMT at 7 days post-booster were Group A, 42.53(95%CI 18.41-66.64); Group B, 23.19(95%CI 17.28-29.10); Group C, 57.75 (95%CI 35.86-79.67).
Conclusions: The 2-dose PrEP regimen of rabies vaccine produces adequate immune response either 0,7 or 0, 28 regimens.

Rotavirus vaccine

Cochrane Database Syst Rev. 2021 Nov 17;11(11):CD008521.
doi: 10.1002/14651858.CD008521.pub6.
Vaccines for preventing rotavirus diarrhoea: vaccines in use
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Abstract
Background: Rotavirus is a common cause of diarrhoea, diarrhoea-related hospital admissions, and diarrhoea-related deaths worldwide. Rotavirus vaccines prequalified by the World Health Organization (WHO) include Rotarix (GlaxoSmithKline), RotaTeq (Merck), and, more recently, Rotasiil (Serum Institute of India Ltd.), and Rotavac (Bharat Biotech Ltd.).
Objectives: To evaluate rotavirus vaccines prequalified by the WHO for their efficacy and safety in children.
Search methods: On 30 November 2020, we searched PubMed, the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (published in the Cochrane Library), Embase, LILACS, Science Citation Index Expanded, Social Sciences Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science & Humanities. We also searched the WHO ICTRP, ClinicalTrials.gov, clinical trial reports from manufacturers' websites, and reference lists of included studies, and relevant systematic reviews.
Selection criteria: We selected randomized controlled trials (RCTs) conducted in children that compared rotavirus vaccines prequalified for use by the WHO with either placebo or no intervention.
Data collection and analysis: Two authors independently assessed trial eligibility and assessed risk of bias. One author extracted data and a second author cross-checked them. We combined dichotomous data using the risk ratio (RR) and 95% confidence interval (CI).

We stratified the analyses by under-five country mortality rate and used GRADE to evaluate evidence certainty.
Main results: Sixty trials met the inclusion criteria and enrolled a total of 228,233 participants. Thirty-six trials (119,114 participants) assessed Rotarix, 15 trials RotaTeq (88,934 participants), five trials Rotasiil (11,753 participants), and four trials Rotavac (8432 participants). Rotarix Infants vaccinated and followed up for the first year of life In low-mortality countries, Rotarix prevented 93% of severe rotavirus diarrhoea cases (14,976 participants, 4 trials; high-certainty evidence), and 52% of severe all-cause diarrhoea cases (3874 participants, 1 trial; moderate-certainty evidence). In medium-mortality countries, Rotarix prevented 79% of severe rotavirus diarrhoea cases (31,671 participants, 4 trials; high-certainty evidence), and 36% of severe all-cause diarrhoea cases (26,479 participants, 2 trials; high-certainty evidence). In high-mortality countries, Rotarix prevented 58% of severe rotavirus diarrhoea cases (15,882 participants, 4 trials; high-certainty evidence), and 27% of severe all-cause diarrhoea cases (5639 participants, 2 trials; high-certainty evidence). Children vaccinated and followed up for two years In low-mortality countries, Rotarix prevented 90% of severe rotavirus diarrhoea cases (18,145 participants, 6 trials; high-certainty evidence), and 51% of severe all-cause diarrhoea episodes (6269 participants, 2 trials; moderate-certainty evidence). In medium-mortality countries, Rotarix prevented 77% of severe rotavirus diarrhoea cases (28,834 participants, 3 trials; high-certainty evidence), and 26% of severe all-cause diarrhoea cases (23,317 participants, 2 trials; moderate-certainty evidence). In high-mortality countries, Rotarix prevented 35% of severe rotavirus diarrhoea cases (13,768 participants, 2 trials; moderate-certainty evidence), and 17% of severe all-cause diarrhoea cases (2764 participants, 1 trial; high-certainty evidence). RotaTeq Infants vaccinated and followed up for the first year of life In low-mortality countries, RotaTeq prevented 97% of severe rotavirus diarrhoea cases (5442 participants, 2 trials; high-certainty evidence). In medium-mortality countries, RotaTeq prevented 79% of severe rotavirus diarrhoea cases (3863 participants, 1 trial; low-certainty evidence). In high-mortality countries, RotaTeq prevented 57% of severe rotavirus diarrhoea cases (6775 participants, 2 trials; high-certainty evidence), but there is probably little or no difference between vaccine and placebo for severe all-cause diarrhoea (1 trial, 4085 participants; moderate-certainty evidence). Children vaccinated and followed up for two years In low-mortality countries, RotaTeq prevented 96% of severe rotavirus diarrhoea cases (5442 participants, 2 trials; high-certainty evidence). In medium-mortality countries, RotaTeq prevented 79% of severe rotavirus diarrhoea cases (3863 participants, 1 trial; low-certainty evidence). In high-mortality countries, RotaTeq prevented 44% of severe rotavirus diarrhoea cases (6744 participants, 2 trials; high-certainty evidence), and 15% of severe all-cause diarrhoea cases (5977 participants, 2 trials; high-certainty evidence). We did not identify RotaTeq studies reporting on severe all-cause diarrhoea in low- or medium-mortality countries. Rotasiil Rotasiil has not been assessed in any RCT in countries with low or medium child mortality. Infants vaccinated and followed up for the first year of life In high-mortality countries, Rotasiil prevented 48% of severe rotavirus diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence), and resulted in little to no difference in severe all-cause diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence). Children vaccinated and followed up for two years In high-mortality countries, Rotasiil prevented 44% of severe rotavirus diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence), and resulted in little to no difference in severe all-cause diarrhoea cases (11,008 participants, 2 trials; high-certainty evidence). Rotavac Rotavac has not been assessed in any RCT in countries with low

or medium child mortality. Infants vaccinated and followed up for the first year of life In high-mortality countries, Rotavac prevented 57% of severe rotavirus diarrhoea cases (6799 participants, 1 trial; moderate-certainty evidence), and 16% of severe all-cause diarrhoea cases (6799 participants, 1 trial; moderate-certainty evidence). Children vaccinated and followed up for two years In high-mortality countries, Rotavac prevented 54% of severe rotavirus diarrhoea cases (6541 participants, 1 trial; moderate-certainty evidence); no Rotavac studies have reported on severe all-cause diarrhoea at two-years follow-up. Safety No increased risk of serious adverse events (SAEs) was detected with Rotarix (103,714 participants, 31 trials; high-certainty evidence), RotaTeq (82,502 participants, 14 trials; moderate to high-certainty evidence), Rotasiil (11,646 participants, 3 trials; high-certainty evidence), or Rotavac (8210 participants, 3 trials; moderate-certainty evidence). Deaths were infrequent and the analysis had insufficient evidence to show an effect on all-cause mortality. Intussusception was rare. AUTHORS' CONCLUSIONS: Rotarix, RotaTeq, Rotasiil, and Rotavac prevent episodes of rotavirus diarrhoea. The relative effect estimate is smaller in high-mortality than in low-mortality countries, but more episodes are prevented in high-mortality settings as the baseline risk is higher. In high-mortality countries some results suggest lower efficacy in the second year. We found no increased risk of serious adverse events, including intussusception, from any of the prequalified rotavirus vaccines.

Typhoid vaccine

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Safety and immunogenicity of Vi-typhoid conjugate vaccine co-administration with routine 9-month vaccination in Burkina Faso: A randomized controlled phase 2 trial

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Abstract

Objectives: In 2017, the World Health Organisation (WHO) pre-qualified a single-dose typhoid conjugate vaccine (TCV) and identified TCV co-administration studies as a research priority. Accordingly, we tested co-administration of Typbar TCV® (Bharat Biotech International) with measles-rubella (MR) and yellow fever (YF) vaccines.

Methods: We conducted a randomized, double-blind, and controlled, phase 2 trial in Ouagadougou, Burkina Faso. Healthy children aged 9-11 months were randomized 1:1 to receive TCV (Group 1) or control vaccine (inactivated polio vaccine (IPV), Group 2). Vaccines were administered intramuscularly with routine MR and YF vaccines. Safety was assessed by (1) local and systemic reactions on days 0, 3, and 7; (2) unsolicited adverse events within 28 days; and (3) serious adverse events (SAEs) within six months after immunization.

Results: We enrolled, randomized, and vaccinated 100 eligible children (49 Group 1 and 51 Group 2). Safety outcomes occurred with similar frequency in both groups: local/solicited reactions (Group 1: 1/49, Group 2: 3/50), systemic/solicited reactions (Group 1: 4/49, Group 2: 9/50), unsolicited adverse events (Group 1: 26/49, Group 2: 33/51), and SAEs (Group 1: 2/49,

Group 2: 3/51). TCV conferred robust immunogenicity without interference with MR or YF vaccines.
Conclusion: TCV can be safely co-administered with MR and YF vaccines to children at the 9-month vaccination visit.

Vitamin A

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Is routine Vitamin A supplementation still justified for children in Nepal? Trial synthesis findings applied to Nepal national mortality estimates
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Abstract
Background: The World Health Organization has recommended Vitamin A supplementation for children in low- and middle-income countries for many years to reduce child mortality. Nepal still practices routine Vitamin A supplementation. We examined the potential current impact of these programs using national data in Nepal combined with an update of the mortality effect estimate from a meta-analysis of randomized controlled trials.
Methods: We used the 2017 Cochrane review as a template for an updated meta-analysis. We conducted fresh searches, re-applied the inclusion criteria, re-extracted the data for mortality and constructed a summary of findings table using GRADE. We applied the best estimate of the effect obtained from the trials to the national statistics of the country to estimate the impact of supplementation on under-five mortality in Nepal.
Results: The effect estimates from well-concealed trials gave a 9% reduction in mortality (Risk Ratio: 0.91, 95% CI 0.85 to 0.97, 6 trials; 1,046,829 participants; low certainty evidence). The funnel plot suggested publication bias, and a meta-analysis of trials published since 2000 gave a smaller effect estimate (Risk Ratio: 0.96, 95% CI 0.89 to 1.03, 2 trials, 1,007,587 participants), with the DEVTA trial contributing 55.1 per cent to this estimate. Applying the estimate from well-concealed trials to Nepal's under-five mortality rate, there may be a reduction in mortality, and this is small from 28 to 25 per 1000 live births; 3 fewer deaths (95% CI 1 to 4 fewer) for every 1000 children supplemented.
Conclusions: Vitamin A supplementation may only result in a quantitatively unimportant reduction in child mortality. Stopping blanket supplementation seems reasonable given these data.

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Vitamin A supplementation for preventing morbidity and mortality in children from six months to five years of age
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Abstract

Background: Vitamin A deficiency (VAD) is a major public health problem in low- and middle-income countries, affecting 190 million children under five years of age and leading to many adverse health consequences, including death. Based on prior evidence and a previous version of this review, the World Health Organization has continued to recommend vitamin A supplementation (VAS) for children aged 6 to 59 months. The last version of this review was published in 2017, and this is an updated version of that review.

Objectives: To assess the effects of vitamin A supplementation (VAS) for preventing morbidity and mortality in children aged six months to five years.

Search methods: We searched CENTRAL, MEDLINE, Embase, six other databases, and two trials registers up to March 2021. We also checked reference lists and contacted relevant organisations and researchers to identify additional studies.

Selection criteria: Randomised controlled trials (RCTs) and cluster-RCTs evaluating the effect of synthetic VAS in children aged six months to five years living in the community. We excluded studies involving children in hospital and children with disease or infection. We also excluded studies evaluating the effects of food fortification, consumption of vitamin A rich foods, or beta-carotene supplementation.

Data collection and analysis: For this update, two review authors independently assessed studies for inclusion resolving discrepancies by discussion. We performed meta-analyses for outcomes, including all-cause and cause-specific mortality, disease, vision, and side effects. We used the GRADE approach to assess the quality of the evidence.

Main results: The updated search identified no new RCTs. We identified 47 studies, involving approximately 1,223,856 children. Studies were set in 19 countries: 30 (63%) in Asia, 16 of these in India; 8 (17%) in Africa; 7 (15%) in Latin America, and 2 (4%) in Australia. About one-third of the studies were in urban/periurban settings, and half were in rural settings; the remaining studies did not clearly report settings. Most studies included equal numbers of girls and boys and lasted about one year. The mean age of the children was about 33 months. The included studies were at variable overall risk of bias; however, evidence for the primary outcome was at low risk of bias. A meta-analysis for all-cause mortality included 19 trials (1,202,382 children). At longest follow-up, there was a 12% observed reduction in the risk of all-cause mortality for VAS compared with control using a fixed-effect model (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.83 to 0.93; high-certainty evidence). Nine trials reported mortality due to diarrhoea and showed a 12% overall reduction for VAS (RR 0.88, 95% CI 0.79 to 0.98; 1,098,538 children; high-certainty evidence). There was no evidence of a difference for VAS on mortality due to measles (RR 0.88, 95% CI 0.69 to 1.11; 6 studies, 1,088,261 children; low-certainty evidence), respiratory disease (RR 0.98, 95% CI 0.86 to 1.12; 9 studies, 1,098,538 children; low-certainty evidence), and meningitis. VAS reduced the incidence of diarrhoea (RR 0.85, 95% CI 0.82 to 0.87; 15 studies, 77,946 children; low-certainty evidence), measles (RR 0.50, 95% CI 0.37 to 0.67; 6 studies, 19,566 children; moderate-certainty evidence), Bitot's spots (RR 0.42, 95% CI 0.33 to 0.53; 5 studies, 1,063,278 children; moderate-certainty evidence), night blindness (RR 0.32, 95% CI 0.21 to 0.50; 2 studies, 22,972 children; moderate-certainty evidence), and VAD (RR 0.71, 95% CI 0.65 to 0.78; 4 studies, 2262 children, moderate-certainty evidence). However, there was no evidence of a difference on incidence of respiratory disease (RR 0.99, 95% CI 0.92 to 1.06; 11 studies, 27,540 children; low-certainty evidence) or hospitalisations due to diarrhoea or pneumonia. There was an increased risk of vomiting within the first 48 hours of VAS (RR 1.97, 95% CI 1.44 to 2.69; 4 studies, 10,541 children; moderate-certainty evidence).

Authors' conclusions: This update identified no new eligible studies and the conclusions remain the same. VAS is associated with a clinically meaningful reduction in morbidity and mortality in children. Further placebo-controlled trials of VAS in children between six months and five years of age would not change the conclusions of this review, although studies that compare different doses and delivery mechanisms are needed. In populations with documented VAD, it would be unethical to conduct placebo-controlled trials.

Vitamin D

(See also Neonates – preterm and low birth weight)

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Daily vitamin D_3 in overweight and obese children and adolescents: a randomized controlled trial

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Abstract

Purpose: To assess the efficacy of different doses of vitamin D_3 on serum 25-hydroxyvitamin D (25(OH)D), intact parathyroid hormone(iPTH), calcium, phosphorus, and alkaline phosphatase concentrations in overweight and obese school-children.

Methods: A total of 378 children and adolescents, 6-13 years of age, with age- and sex-specific body mass index(BMI) Z-score ≥ 1(according to the World Health Organization criteria) were allocated to receive 600, 1000, and 2000 IU vitamin D_3/days. 25(OH)D, iPTH, calcium, phosphorus, and alkaline phosphatase concentrations were measured at baseline, 6, and 12 months. In this intention-to-treat analysis, we fitted a linear mixed effect model involving a random effect of participants within treatment groups and fixed effects of dose, time, and their interactions.

Results: Mean(SD) of age and BMI Z-score were 9.3 (1.7) years and 2.55 (0.73), respectively. The median (IQR) for 25(OH)D was 11.5 (8.9), 11.7 (10.5), 12.2 (10.2) ng/mL (28.75, 29.25, and 30.50 nmol/L) at baseline and 23.1 (8.0), 25.6 (8.3), 28.6 (10.4) ng/mL (57.75, 64.00, and 71.50 nmol/L) at the end of 12 months in 600, 1000, and 2000 IU, respectively (p values for dose, time, and the interaction being < 0.0001, < 0.0001,and 0.082, respectively). Prevalence of vitamin D deficiency (< 20 ng/mL) was 80.2, 77.5, and 75.5% in 600, 1000, and 2000 IU groups at baseline, respectively, which decreased to 34, 18.4, and 7.5%, respectively, at 12 months. Patterns of iPTH, calcium, phosphorus, and alkaline phosphatase response over time did not differ significantly among groups (p values = 0.452, 0.670, 0.377, 0.895, respectively).

Conclusions: Increases in 25(OH)D concentration were found with supplementation of 1000 and 2000 IU, compared with 600 IU/days, whereas there was no evidence of iPTH suppression or change in serum calcium, phosphorus, and alkaline phosphatase among children with excess weight.

Yaws

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Trial of Three Rounds of Mass Azithromycin Administration for Yaws Eradication

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Abstract

Background: *Treponema pallidum* subspecies *pertenue* causes yaws. Strategies to better control, eliminate, and eradicate yaws are needed.

Methods: In an open-label, cluster-randomized, community-based trial conducted in a yaws-endemic area of Papua New Guinea, we randomly assigned 38 wards (i.e., clusters) to receive one round of mass administration of azithromycin followed by two rounds of target treatment of active cases (control group) or three rounds of mass administration of azithromycin (experimental group); round 1 was administered at baseline, round 2 at 6 months, and round 3 at 12 months. The coprimary end points were the prevalence of active cases of yaws, confirmed by polymerase-chain-reaction assay, in the entire trial population and the prevalence of latent yaws, confirmed by serologic testing, in a subgroup of asymptomatic children 1 to 15 years of age; prevalences were measured at 18 months, and the between-group differences were calculated.

Results: Of the 38 wards, 19 were randomly assigned to the control group (30,438 persons) and 19 to the experimental group (26,238 persons). A total of 24,848 doses of azithromycin were administered in the control group (22,033 were given to the participants at round 1 and 207 and 2608 were given to the participants with yaws-like lesions and their contacts, respectively, at rounds 2 and 3 [combined]), and 59,852 doses were administered in the experimental group. At 18 months, the prevalence of active yaws had decreased from 0.46% (102 of 22,033 persons) at baseline to 0.16% (47 of 29,954 persons) in the control group and from 0.43% (87 of 20,331 persons) at baseline to 0.04% (10 of 25,987 persons) in the experimental group (relative risk adjusted for clustering, 4.08; 95% confidence interval [CI], 1.90 to 8.76). The prevalence of other infectious ulcers decreased to a similar extent in the two treatment groups. The prevalence of latent yaws at 18 months was 6.54% (95% CI, 5.00 to 8.08) among 994 children in the control group and 3.28% (95% CI, 2.14 to 4.42) among 945 children in the experimental group (relative risk adjusted for clustering and age, 2.03; 95% CI, 1.12 to 3.70). Three cases of yaws with resistance to macrolides were found in the experimental group.

Conclusions: The reduction in the community prevalence of yaws was greater with three rounds of mass administration of azithromycin at 6-month intervals than with one round of mass administration of azithromycin followed by two rounds of targeted treatment. Monitoring for the emergence and spread of antimicrobial resistance is needed.