RANDOMISED TRIALS IN CHILD AND ADOLESCENT HEALTH IN DEVELOPING COUNTRIES

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Please send suggestions about this booklet to:

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

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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**

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 322 trial publications were identified. These were conducted in countries from all regions of the world. Several trials from 2018-19 will lead to significant changes in child health recommendations. This year four studies showed reductions in mortality. These studies are marked *** in the book. Where there were no trials this year under a certain sub-heading I have left the heading in the book, to indicate the lack of trials. Many trials could be listed under several sub-headings, and there is overlap in the sub-headings, so there may be fewer gaps than is first apparent.

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

Please feel free to distribute this booklet to your colleagues. The previous editions (2002-2018) are available at: **www.hospitalcareforchildren.org**

A brief summary of some of the important results in 2018-19

- In primary and secondary schools in Malawi, teaching empowerment and self-defence to school-age girls reduced the risk of sexual assault and victimisation.

- In South Africa in a trial of community treatment supporter among 97 adolescents living with HIV, the 47 who had community adolescent treatment supporters were 3 times more likely to adhere to treatment, were more likely to link to services, and had greater confidence, self-esteem and quality of life compared with the control arm.

- In India among 50 children undergoing sevoflourane induction for anaesthesia, low flow gas at 1L/min was as effective as high or standard gas flows of 6 L/min, reducing the cost and environmental effects of volatile anaesthetics.

- ******* In a pooled analysis of all trials of mass drug administration with azithromycin in 4 countries in sub-Saharan Africa (Ethiopia, Malawi, Niger, and Tanzania), azithomycin reduced all-cause mortality. However the major effect was in Niger, where baseline mortality risk was very high. In a follow-up of the original MORDOR trial, the beneficial effect of azithromycin on child mortality persisted for 3 years, and in the communities originally given placebo but in the third year given azithromycin child mortality decreased by 13%.

- In Burkina Faso, preschool children with pre-existing morbidity treated with 5 days of amoxycillin gained significantly more weight (an additional 300g after one month) compared with both the placebo sibling and placebo household controls. No effect on anthropometrics was seen in children treated with azithromycin or cotrimoxazole.

- In Thailand and Myanmar, among 2419 febrile children attending primary care, testing for C-reactive protein with a threshold of 40 mg/L for antibiotic prescribing resulted in a 20% reduction in antibiotic prescribing.

- A family-based economic strengthening intervention for 1410 school children who were orphaned because of HIV in 48 schools in Uganda reduced indices of poverty at 12 months, and significantly improved adolescents' mental health outcomes at 2 years. Anti-poverty programs should not solely be measured on their ability to improve household incomes.

- In a meta-analysis of trials of HIV-positive people without pre-existing cryptococcal infection, prophylaxis with fluconazole reduced the risk of developing cryptococcal disease (RR 0.29, 95% CI 0.17 to 0.49; 7 trials, 5000 participants), and reduced deaths due to cryptococcal disease (RR 0.29, 95% CI 0.11 to 0.72; 5 trials, 3813 participants. There was no effect on all-cause mortality. Fluconazole was well tolerated and did not seem to lead to more resistant candida infections.

- In health care clinics in Bangladesh a trial involving 1737 underweight children of a program which taught parents how to support their child's development through play and interactions significantly improved children's cognition, language, motor skills, and behaviour ratings, but had no significant effect on growth.

- Among 1273 children aged 12-18 months, living in 120 villages in India, household and family adversities were associated with lower cognitive, language, and other development scores, and lower weight and height, and there a gradient related to the number of adversities faced by the child.

- Among 2,363 child cases of diarrhoea attending 118 community health workers in Uganda, giving oral rehydration solution (ORS) free resulted in substantially more ORS coverage (74-77%) than if ORS was sold (56%). This is not surprising, but in most of the world parents still have to pay for ORS, which based on this trial is one major barrier to use that can be overcome.

- In a meta-analysis of trials of treatment of Entamoeba histolytica (amoebic dysentery), tinidazole was more effective than metronidazole for reducing clinical failure (RR 0.28, 95% CI 0.15 to 0.51; 477 participants, eight trials) and associated with fewer adverse events (RR 0.65, 95% CI 0.46 to 0.92; 477 participants, 8 trials).

- In a cluster RCT in 28 rural villages in Ethiopia, the use of solar disinfection of water resulted in a 40% reduction in diarrhoea incidence in children under 5 years of age, and in a cluster RCT in Pakistan of fly reduction strategies (insecticide spraying in the first two years and baited fly traps in the third year) diarrhoea incidence was also reduced.

- In Rwanda, among over 1500 households from clusters randomised to receiving water filters and portable biomass-burning natural draft rocket-style cook stoves, the prevalence of reported child diarrhoea was reduced by 29% and reported child ARI by 25%.

- Among 118 children in Bangladesh with idiopathic focal, generalized, or focal with secondary generalised epilepsy randomised to levetiracetam or phenobarbitone, levetiracetam was more effective than phenobarbitone in achieving seizure remission at 6 and 9 months (66% vs 44%). And in another trial of 100 Indian children with acute seizures, levetiracetam (30mg/kg) and phenytoin (20mg/kg) were equally effective in stopping seizures and reducing recurrence in the first 24 hours.

- In Indian children with epilepsy newly treated with antiepileptic drugs, vitamin D (60,000 IU vitamin D3 orally under direct supervision) maintained baseline 25(OH) vitamin D levels, whereas control children became vitamin D deficient.

- In 60 villages of rural Burkina Faso there was a strong association between being seropositive for cysticercosis and the prevalence of epilepsy and severe chronic headaches.

- Large community-based trials of water, sanitation and hygiene in Zimbabwe, Bangladesh and Kenya showed modest or minimal effects on stunting and anaemia and other indices of child development. When accompanied by programs for infant and young child feeding there were reductions in stunting and anaemia.

- In Shimla district in India where teachers were taught to identify sore throat and rheumatic heart disease and refer to hospital for echocardiographic assessment, the

reporting increased but the yield of patients with heart disease was no different from that in a control group of schools, where parents sought care in the usual way if their child was unwell.

- In Malawi, Uganda and Tanzania, infants of HIV-positive mothers enrolled in a web-based intervention linking health care providers of early infant diagnosis, laboratory technicians, and mothers and infants, were 3 times more likely to receive complete early infant diagnosis services compared with those assigned standard of care.

- In Kenya, HIV-positive pregnant women who receive individualized health education, retention/adherence support, appointment reminders, and missed visit tracking by a lay health counsellor were significantly more likely to be retained in the HIV care system (19% attrition vs 28% for standard care).

- In a trial in 3 schools in Kenya, giving 300ml of papaya seed fortified maize-flour porridge daily at school was highly effective at reducing Ascaris lumbracoides worm infestation (reduction of 63% at 2 months), compared with schools that gave non-fortified maize-flour porridge plus albendazole, whereas children in control schools who were given non-fortified porridge without albendazole had an increase in worm infection. Children who ate papaya seed fortified porridge had increased haemoglobin: a greater increase (+2g/dL) than those given albendazole (+1g/dL), and they also had reduced ringworm infection.

- In another trial of deworming in Kenya, involving 120 community clusters serving 150 000 people, biannual community-wide treatment with albendazole was more effective in reducing hookworm prevalence and intensity than school-based treatment: risk ratio 0·46 (0·33-0·63; p<0·001), and the effect of community-wide treatment was equitable in coverage and effects across social groups.

- Among 61 Indian children with frequently relapsing nephrotic syndrome (FRNS) patients who were weaned to prednisolone at 0.2-0.3 mg/kg daily had a much lower rate of relapse over one year than children weaned to alternate day prednisolone 0.5-0.7 mg/kg.

- In Indian children with difficult to treat nephrotic syndrome where bone mineral loss is a risk because of prolonged steroid use, giving 3-monthly vitamin D either 1000 or 400 IU/day was equally effective for preventing bone loss.

- In 40 villages in Iran containing on average 160 children, community-wide use of insecticide-impregnated collars for dogs - the reservoir of *Leishmania infantum* – significantly reduced infantile clinical visceral leishmaniosis, compared to villages where dog collars were used that did not contain insecticide.

- Among 1980 children in Burkina Faso, where permethrin resistance among malaria is increasing, use of bed-nets containing permethrin, a pyrethroid, and pyriproxyfen, an insect growth regulator, was significantly more effective in reducing clinical malaria episodes than traditional permethrin-only long-lasting insecticide treated nets.

- In both Papua New Guinea and Malawi there was evidence that there is poor adherence to intermittent chemoprophylaxis with anti-malarial drugs, when these agents are given at home by parents; whether given to parents at the time of immunisation (PNG), or on discharge from hospital after an illness (Malawi). In Malawi, training community health workers to remind parents to give these treatments was not as effective as anticipated.

- Among over 2000 children in 24 villages in Senegal, seasonal malaria chemoprophylaxis (SMC) delivered with community-case management markedly reduced episodes of RDT-confirmed malaria: there were 1,472 RDT-confirmed malaria cases in the control villages and 270 in the SMC villages, and SMC lead to higher levels of haemoglobin in the villages receiving seasonal malaria chemoprophylaxis at the end of the transmission season.

- In Laos, mass drug administration (MDA) with dihydroartemisinin-piperaquine with a single low dose of primaquine added to basic malaria control, including insecticide-treated bed nets and early diagnosis and treatment, and the prevalence of asymptomatic P. falciparum infections decreased by 85% after MDA (from 4.8% at baseline to 0.7% at 12 month. This compared to a decrease of 33% in P. falciparum prevalence in the same time in control villages. On the other hand, in another trial of MDA in a low transmission area in Zanzibar there was no difference in malaria case incidence or parasite prevalence between the control and intervention villages 6 months post-MDA.

- In two studies involving 534 children in Rwanda and 507 children in Tanzania with uncomplicated malaria, treated with dihydroartemisinin-piperaquine or artemether-lumefantrine, both agents were highly effective in parasite reduction and clinical cure.

- Among 109 Cambodian children with uncomplicated malaria treated with dihydroartemisinin-piperaquine plus a single low dose of primaquine, the haemoglobin at 7 days was lower if they Glucose 6-Phosphate Dehydrogenase Deficiency (G6PD): 10.9 vs. 12.05 g/dL, but the difference was modest. Low-dose primaquine 0.25 mg/kg body weight in falciparum-infected patients is safe and may block malaria transmission and help eliminate multidrug resistant Plasmodium falciparum.

- In a study of infants in Tanzania, presence of inflammation as evidenced by a high C-reactive protein and low insulin-like growth factor were associated with stunting, even as early as 6 weeks of age.

- In antenatal clinics in Nigeria, intermittent screening for malaria with an RDT and treatment with artemether-lumefantrine only if positive was more effective than intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (S-P) given to all pregnant women. Screening and treating positive cases was more effective in reducing third-trimester parasitaemia, and was associated with a lower risk of low birth weight. In another trial in Nigeria, 3 doses of intermittent preventive treatment with S-P was more effective than 2 doses in reducing the risk of parasitaemia and placental malaria. In Malawi chloroquine given intermittently or weekly was not superior to S-P, and chloroquine was poorly tolerated compared to S-P.

- Among preterm newborns in India, delayed cord clamping to 120 seconds after birth, compared with early cord clamping within 30 seconds of birth, resulted in a significantly

higher haematocrit and no increase in serum bilirubin, at 7 days of life. In another trial in India delayed cord clamping in newborns >35 weeks gestation significantly increased serum ferritin and reduced the risk of iron deficiency at 3 months of age, without any increased risk of polycythaemia. In another trial in India, among preterm babies, umbilical cord milking resulted in substantially higher Hb and ferritin levels at 6 weeks of age.

- ******* A meta-analysis of five studies from developing countries involving 129,293 newborns showed that chlorhexidine cord application reduces neonatal sepsis by 32%, severe sepsis by 77% and neonatal mortality by 13%, compared to dry cord care.

- In India, in 2 trials of early full enteral feeding of very low birthweight babies, involving 180 babies 1000-1499g) and 131 babies 750-1125g, early full enteral feeding was associated with fewer episodes of feed intolerance and clinical sepsis, fewer days on intravenous fluid, shorter duration of hospital stay, and no difference in rates of necrotising enterocolitis compared with neonates whose feeds were graded up slowly with a combination of conservative enteral feeding and IV fluids.

- In a meta-analysis six trials including 436 term neonates with birth asphyxia who received a single dose of theophylline there was a 60% reduction (RR: 0.40; 95% CI 0.3 to 0.54) in the incidence of acute kidney injury, compared with controls.

- In 174 Nigerian neonates with moderate-severe hyperbilirubinaemia, filtered sunlight using commercial tinting films that transmitted effective phototherapeutic light, blocked ultraviolet light, and reduced infrared radiation was as effective as intensive electric phototherapy.

- Among 501 Zambian infants fortification of complementary food (a soya-maize-based porridge) with locally grown *spirulina platensis* compared to a soya-maize-based porridge without fortification for 1 year less likely to develop a cough and were more likely to be able to walk alone at 15 months than infants in the control group.

- Among 140 Indian girls and boys aged 12-16 who were randomised to consume iron-bio-fortified or conventional pearl millet, the consumption of bio-fortified pearl millet resulted in greater improvement in attention and memory. Reaction time decreased twice as much from in those consuming bio-fortified compared with conventional pearl millet on attention tasks.

- A meta-analysis of 17 studies of lipid-based nutrient supplements (LNS) involving 23,000 children showed a benefit of LNS plus complimentary feeding on moderate and severe stunting, moderate wasting and anaemia, and a single study of 750 South African infants 6-12 months showed bio-fortified LNS improved locomotor development.

- In Brazil where health care workers were trained in Infant and Young Child Feeding, children at 1 year age had marginally improved dietary diversity and meal frequency, but although only if children attended more than seven follow-up appointments during the first year of life.

- In India 2 studies of new anti-emetic agents, palonosetron and fosaprepitant in the management of chemotherapy-induced vomiting showed them to be effective, but no more so than the combination of ondansetron and dexamethasone.

- In 74 Government schools in India, the SEHER school health promotion intervention showed substantial beneficial effects on school climate and health-related outcomes when delivered by lay counsellors. These benefits included reduced depression, bullying, violence victimisation, attitudes to gender equity, and knowledge of reproductive and sexual health. This program was not effective when delivered by teachers.

- ******* Among over 4000 children in India, active surveillance for tuberculosis increased the case-finding rates for probable TB and was associated with reduced all-cause mortality, mostly attributable to reduction of death from pneumonia/respiratory infections (OR 0.34, 95% CI 0.14 to 0.80).

- In a meta-analysis of studies to prevent tuberculosis in contacts, a 3-month regimen of rifapentine plus isoniazid (3-HP) was as effective as 6 or 9 months of isoniazid, and reduced the risk of hepatotoxicity.

- In a multinational influenza vaccine trial in 13 countries in Europe, Central America, and Asia, involving 12000 children, vaccine efficacy was 63% (97·5% CI 52-72) against moderate-to-severe influenza and 50% (42-57) against all influenza. In another influenza trial in Latin America, Asia, Africa, and Europe involving 5800 children vaccine efficacy was 51% (97% CI, 37-62%) against influenza caused by any A or B type and 68% (97% CI, 47-82%) against influenza caused by vaccine-like strains.

- A meta-analysis of different rotavirus vaccine trials showed that in high-mortality countries, RV1 prevented 63% of severe rotavirus diarrhoea cases (RR 0.37, 95% CI 0.23 to 0.60; 6114 participants, 3 trials), and 27% of severe all-cause diarrhoea cases (RR 0.73, 95% CI 0.56 to 0.95; 5639 participants, 2 trials). RV5 prevented 57% of severe rotavirus diarrhoea (RR 0.43, 95% CI 0.29 to 0.62; 5916 participants, 2 trials), but there was probably little difference between RV5 vaccine and placebo for severe all-cause diarrhoea (RR 0.80, 95% CI 0.58 to 1.11). In a factorial trial in rural Zimbabwe, rotavirus vaccine immunogenicity was greater in infants whose households received improved water and sanitation. This may partly account for the lower effectiveness of rotavirus vaccines in low income countries.

- In a reanalysis of neonatal vitamin A (NVAS) studies, NVAS reduced infant mortality in South Asia, in contexts where the prevalence of maternal vitamin A deficiency is moderate to severe and early infant mortality is high (>30/1000). However NVAS had no beneficial effect on infant survival in Africa, or in contexts where the prevalence of maternal vitamin A deficiency is low, or where early infant mortality is low.

- ******* Among 196 very low birth weight babies in India who required respiratory support at 24 hours of age, the composite incidence of all-cause mortality and oxygen requirement for 28 days was significantly lower in vitamin A group: relative risk (95% confidence interval), 0.440 (0.229-0.844).

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

I have been liberal in what is included as an RCT. 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.

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 **3085 trial publications** summarised in the 17 editions of this book. It is interesting to see the evolution of trials each year. It is encouraging to see the evaluation of the developmental, psychological and mental health effects of interventions. Also encouraging is the increased number of trials that include adolescents; particularly this year trials of interventions to reduce violence against 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 such as epilepsy, asthma, and neurodevelopmental problems; and quality improvement research on how best to provide acute and chronic care for children in remote health care settings. However some studies this year help to fill these gaps.

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

Trevor Duke
July 2019

Acknowledgements
Thanks to Poh Chua for helping refine the search strategy this year.

Search strategy

Pubmed Advanced strategy, search: ("Developing Countries"[Mesh] OR (austere OR limited resource* OR "resource limited" OR low resource* OR transitioning econom* OR lami countr* OR transitional countr* OR "low gdp" OR "low gnp" OR "low gross domestic" OR "low gross national" OR ((emerging OR developing OR "low income" OR "middle income" OR (low AND middle) OR underdeveloped OR "under developed" OR under-developed OR underserved OR "under served" OR under-served OR (less-developed) OR deprived OR poor) AND (countr* OR nation* OR econom* OR population OR world)) OR "third world" OR LMIC OR LMICs) OR "Africa"[Mesh] OR "caribbean region"[Mesh] OR "central america"[Mesh] OR "latin america"[Mesh] OR "mexico"[Mesh] OR "south america"[Mesh] OR "europe, eastern"[Mesh] OR "indian ocean islands"[Mesh] OR "pacific islands"[Mesh] OR "New Guinea"[Mesh] OR India OR Africa OR Asia OR South-America OR Papua-New-Guinea OR Pacific) AND (newborn* OR new-born* OR baby OR babies OR neonat* OR neo-nat* OR infan* OR boy OR boys OR girl OR girls OR child OR children OR childhood OR pediatric* OR paediatric* OR adolescen* OR youth OR youths OR teen OR teens OR teenage*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized-controlled-trial*[tiab] OR randomised-controlled-trial*[tiab] OR randomized-trial*[tiab] OR randomised-trial*[tiab] NOT (animals[mh] NOT humans[mh])): Publication date between July 1 2018 and June 30 2019.

Acute respiratory infection

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

Prevention of pneumonia

(see Vaccines – Pneumococcal)

Treatment of pneumonia

Implement Sci. 2019 Mar 4;14(1):20. doi: 10.1186/s13012-019-0868-4. (Open access available)

Effect of enhancing audit and feedback on uptake of childhood pneumonia treatment policy in hospitals that are part of a clinical network: a cluster randomized trial.

Ayieko P, Irimu G, Ogero M, Mwaniki P, Malla L, Julius T, Chepkirui M, Mbevi G, Oliwa J, Agweyu A, Akech S, Were F, English M
Kenya

BACKGROUND:
The World Health Organization (WHO) revised its clinical guidelines for management of childhood pneumonia in 2013. Significant delays have occurred during previous introductions of newguidelines into routine clinical practice in low- and middle-income countries (LMIC). We therefore examined whether providing enhanced audit and feedback as opposed to routine standard feedback might accelerate adoption of the new pneumonia guidelines by clinical teams within hospitals in a low-income setting.

METHODS:
In this parallel group cluster randomized controlled trial, **12 hospitals were assigned to either enhanced feedback (n = 6 hospitals) or standard feedback (n = 6 hospitals)** using restricted randomization. The standard (network) intervention delivered in both trial arms included support to improve collection and quality of patient data, provision of mentorship and team management training for pediatricians, peer-to-peer networking (meetings and social media), and multimodal (print, electronic) bimonthly hospital specific feedback reports on multiple indicators of evidence guideline adherence. In addition to this network intervention, the enhanced feedback group received a monthly hospital-specific feedback sheet targeting pneumonia indicators presented in multiple formats (graphical and text) linked to explicit performance goals and action plans and specific email follow up from a network coordinator. At the start of the trial, all hospitals received a standardized training on the new guidelines and printed booklets containing pneumonia treatment protocols. The primary outcome was the proportion of children admitted with indrawing and/or fast-breathing pneumonia who were correctly classified using newguidelines and received correct antibiotic treatment (oral amoxicillin) in the first 24 h. The secondary outcome was the proportion of correctly classified and treated children for whom clinicians changed treatment from oral amoxicillin to injectable antibiotics.

RESULTS:

The trial included 2299 childhood pneumonia admissions, 1087 within the hospitals randomized to enhanced feedback intervention, and 1212 to standard feedback. The proportion of children who were correctly classified and treated in the first 24 h during the entire 9-month period was 38.2% (393 out of 1030) and 38.4% (410 out of 1068) in the enhanced feedback and standard feedback groups, respectively (odds ratio 1.11; 95% confidence interval [CI] 0.37-3.34; P = 0.855). However, in exploratory analyses, there was evidence of an interaction between type of feedback and duration (in months) since commencement of intervention, suggesting a difference in adoption of pneumonia policy over time in the enhanced compared to standard feedback arm (OR = 1.25, 95% CI 1.14 to 1.36, P < 0.001).

CONCLUSIONS:
Enhanced feedback comprising increased frequency, clear messaging aligned with goal setting, and outreach from a coordinator did not lead to a significant overall effect on correct pneumonia classification and treatment during the 9-month trial. There appeared to be a significant effect of time (representing cumulative effect of feedback cycles) on adoption of the new policy in the enhanced feedback compared to standard feedback group. Future studies should plan for longer follow-up periods to confirm these findings.

Cochrane Database Syst Rev. 2019 Jan 2;1:CD010277. doi: 10.1002/14651858.CD010277.pub3. (Open access available)

Chest physiotherapy for pneumonia in children.

Chaves GS, Freitas DA, Santino TA, Nogueira PAM, Fregonezi GA, Mendonça KM.
Brazil

BACKGROUND:
Pneumonia is a lung infection that causes more deaths in children aged under five years than any other single cause. Chest physiotherapy is widely used as adjuvant treatment for pneumonia. Physiotherapy is thought to help remove inflammatory exudates, tracheobronchial secretions, and airway obstructions, and reduce airway resistance to improve breathing and enhance gas exchange. This is an update of a review published in 2013.

OBJECTIVES:
To assess the effectiveness of chest physiotherapy with regard to time until clinical resolution in children (from birth to 18 years) of either gender with any type of pneumonia.

SEARCH METHODS:
We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (22 February 2018), Embase (22 February 2018), CINAHL (22 February 2018), LILACS (22 February 2018), Web of Science (22 February 2018), and PEDro (22 February 2018). We also searched clinical trials registers (ClinicalTrials.gov and WHO ICTRP) to identify planned, ongoing, and unpublished trials.

SELECTION CRITERIA:
We included randomised controlled trials (RCTs) that compared any type of chest physiotherapy with no chest physiotherapy for children with pneumonia.

DATA COLLECTION AND ANALYSIS:
We used standard Cochrane methodological procedures. The primary outcomes of interest were mortality, duration of hospital stay, and time to clinical resolution. We used Review Manager 5 software to analyse data and GRADE to assess the quality of the evidence for each outcome.

MAIN RESULTS:
We included three new RCTs for this update, for a total of six included RCTs involving 559 children aged from 29 days to 12 years with pneumonia who were treated as inpatients. Pneumonia severity was described as moderate in one trial, severe in two trials, and was not stated in three trials. The studies assessed five different interventions: effects of conventional chest physiotherapy (3 studies, 211 children), positive expiratory pressure (1 study, 72 children), continuous positive airway pressure (CPAP) (1 study, 94 children), bubble CPAP (bCPAP) (1 study, 225 children), and assisted autogenic drainage (1 studies, 29 children). The included studies were conducted in Bangladesh, Brazil, China, Egypt, and South Africa. The studies were overall at low risk of bias. Blinding of participants was not possible in most studies, but we considered that the outcomes were unlikely to be influenced by the lack of blinding.All included studies evaluated mortality. However, three studies assessed mortality as an outcome, and only one study of bCPAP reported that deaths occurred. Three deaths occurred in children in the physiotherapy group (N = 79) and 20 deaths in children in the control group (N = 146) (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.08 to 0.90; 559 children; low-quality evidence). It is uncertain whether chest physiotherapy techniques (bCPAP, assisted autogenic drainage, and conventional chest physiotherapy) reduced hospital stay duration (days) (mean difference (MD) 0.10, 95% CI -0.56 to 0.76; 4 studies; low-quality evidence).There was variation among clinical parameters used to define clinical resolution. Two small studies found no difference in resolution of fever between children in the physiotherapy (conventional chest physiotherapy and assisted autogenic drainage) and control groups. Of five studies that considered peripheral oxygen saturation levels, only two reported that use of chest physiotherapy (CPAP and conventional chest physiotherapy) showed a greater improvement in peripheral oxygen saturation levels. However, it was unclear whether respiratory rate (breaths/min) improved after conventional chest physiotherapy (MD -2.25, 95% CI -5.17 to 0.68; 2 studies, 122 children; low-quality evidence). Two studies assessed adverse events (number of events), but only one study reported any events (RR 1.28, 95% CI 0.98 to 1.67; 2 studies, 254 children; low-quality evidence).

AUTHORS' CONCLUSIONS:
We could draw no reliable conclusions concerning the use of chest physiotherapy for children with pneumonia due to the small number of included trials with differing study characteristics and statistical presentation of data. Future studies should consider the following key points: appropriate sample size with adequate power to detect expected differences, standardisation of chest physiotherapy techniques, appropriate outcomes (such as duration of leukocytosis, and airway clearance), and adverse effects.

Cochrane Database Syst Rev. 2018 Jul 19;7:CD011597. doi: 10.1002/14651858.CD011597.pub2. (Open access available)

Vitamin D as an adjunct to antibiotics for the treatment of acute childhood pneumonia.

Das RR, Singh M, Naik SS.
India

BACKGROUND:
Children with acute pneumonia may be vitamin D deficient. Clinical trials have found that prophylactic vitamin D supplementation decreases the risk of developing pneumonia in children. Data on the therapeutic effects of vitamin D in acute childhood pneumonia are limited.

OBJECTIVES:
To evaluate the efficacy and safety of vitamin D supplementation as an adjunct to antibiotics for the treatment of acute childhood pneumonia.

SEARCH METHODS:
We searched CENTRAL (2017, Issue 7), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; Ovid MEDLINE Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE Daily and Ovid MEDLINE (1946 to July Week 4, 2017); and Embase (2010 to 28 July 2017). We also searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) on 28 July 2017. There were no language restrictions.

SELECTION CRITERIA:
Randomised controlled trials (RCTs) including children (aged over one month and up to five years) hospitalised with acute community-acquired pneumonia, as defined by the WHO acute respiratory infection guidelines, that compared vitamin D supplementation with control.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed studies for inclusion and extracted data. For dichotomous data, we extracted the number of participants experiencing the outcome and the total number of participants in each treatment group. For continuous data, we used the arithmetic mean and standard deviation (SD) for each treatment group together with numbers of participants in each group. We used standard methodological procedures expected by Cochrane.

MAIN RESULTS:
We included seven RCTs conducted in low-income countries that involved 1529 children (780 with pneumonia and 749 with severe or very severe pneumonia). Four studies used a single 100,000 IU dose of vitamin D_3 at the onset of illness or within 24 hours of hospital admission;

two used a daily dose of oral vitamin D_3 (1000 IU for children aged up to one year and 2000 IU for children aged over one year) for five days; and one used a daily dose of oral vitamin D_3 (50,000 IU) for two days. One study reported microbiological and radiological diagnosis of pneumonia.The effects of vitamin D on outcomes were inconclusive when compared with control: time to resolution of acute illness (hours) (mean difference (MD) -0.95, 95% confidence interval (CI) -6.14 to 4.24; 3 studies; 935 children; low-quality evidence) mortality rate (risk ratio (RR) 0.97, 95% CI 0.06 to 15.28; 1 study; 193 children; very low-quality evidence); duration of hospitalisation (MD 0.49, 95% CI -8.41 to 9.4; 4 studies; 835 children; very low-quality evidence) and time to resolution of fever (MD 1.66, 95% CI -2.44 to 5.76; 4 studies; 584 children; very low-quality evidence). No major adverse events were reported. The GRADE assessment found very low-quality evidence (due to serious study limitations, inconsistencies, indirectness, and imprecision) for all outcomes except time to resolution of acute illness.One study was funded by the New Zealand Aid Corporation; one study was funded by an institutional grant; and five studies were unfunded.

AUTHORS' CONCLUSIONS:
We are uncertain as to whether vitamin D has an important effect on outcomes because the results were imprecise. No major adverse events were reported. We assessed the quality of the evidence as very low to low. Several trials are ongoing and may provide additional information.

Oxygen therapy and CPAP for ALRI

PLoS One. 2019 Apr 15;14(4):e0213937. doi: 10.1371/journal.pone.0213937. eCollection 2019. (Open access available)

Retrospective study on the usefulness of pulse oximetry for the identification of young children with severe illnesses and severe pneumonia in a rural outpatient clinic of Papua New Guinea.

Blanc J, Locatelli I, Rarau P, Mueller I, Genton B, Boillat-Blanco N, Gehri M, Senn N.
Papua New Guinea, Switzerland, Australia

OBJECTIVE:
This secondary analysis of data of a randomized controlled trial (RCT) retrospectively investigated the performance of pulse oximetry in identifying children with severe illnesses, with and without respiratory signs/symptoms, in a cohort of children followed for morbid episodes in an intervention trial assessing the efficacy of Intermittent Preventive Treatment for malaria in infants (IPTi) in Papua New Guinea (PNG) from June 2006 to May 2010.

SETTING:
The IPTi study was conducted in a paediatric population visiting two health centres on the north coast of PNG in the Mugil area of the Sumkar District.

PARTICIPANTS:

A total of 669 children visited the clinic and a total of 1921 illness episodes were recorded. Inclusion criteria were: age between 3 and 27 months, full clinical record (signs/symptoms) and pulse oximetry used systematically to assess sick children at all visits. Children were excluded if they visited the clinic in the previous 14 days.

OUTCOMES:
The outcome measures were severe illness, severe pneumonia, pneumonia, defined by the Integrated Management of Childhood Illness (IMCI) definitions, and hospitalization.

RESULTS:
Out of 1921 illness episodes, 1663 fulfilled the inclusion criteria. A total of 139 severe illnesses were identified, of which 93 were severe pneumonia. The ROC curves of pulse oximetry (continuous variable) showed an AUC of 0.63, 0.68 and 0.65 for prediction of severe illness, severe pneumonia and hospitalization, respectively. **Pulse oximetry allowed better discrimination between severe and non-severe illness, severe and non-severe pneumonia, admitted and non-admitted patients, in children ≤12-months of age relative to older patients**. For the threshold of peripheral arterial oxygen saturation ≤ 94% measured by pulse oximetry (SpO2), unadjusted odds ratios for severe illness, severe pneumonia and hospitalization were 6.1 (95% Confidence Interval (CI) 3.9-9.8), 8.5 (4.9-14.6) and 5.9 (3.4-10.3), respectively.

CONCLUSION:
Pulse oximetry was helpful in identifying children with severe illness in outpatient facilities in PNG. A SpO2 of 94% seems the most discriminative threshold. Considering its affordability and ease of use, pulse oximetry could be a valuable additional tool assisting the decision to admit for treatment.

Cochrane Database Syst Rev. 2019 Jan 31;1:CD010473. doi: 10.1002/14651858.CD010473.pub3. (Open access available)

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

Jat KR, Mathew JL.
India

BACKGROUND:
Acute bronchiolitis is one of the most frequent causes of emergency department visits and hospitalisation in children. 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.

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 (2017, Issue 12), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to December, 2017), Embase (1974 to December 2017), CINAHL (1981 to December 2017), and LILACS (1982 to December 2017) in January 2018.

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.

MAIN RESULTS:
We included three studies with a total of 122 children (62/60 in intervention/control arms) aged up to 12 months that investigated nasal CPAP compared with supportive (or "standard") therapy. We included one new trial (72 children) that contributed data to the assessment of respiratory rate and need for mechanical ventilation for this update. The included studies were single-centre trials conducted in France, the UK, and India. Two studies were parallel-group RCTs and one was a cross-over RCT. The evidence provided by the included studies was low quality; we assessed 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 imprecision around the effect estimate (3 RCTs, 122 children; risk ratio (RR) 0.69, 95% confidence interval (CI) 0.14 to 3.36; low-quality evidence). None of the trials measured time to recovery. Limited, low-quality evidence indicated that CPAP decreased respiratory rate (2 RCTs, 91 children; mean difference (MD) -3.81, 95% CI -5.78 to -1.84). Only one trial measured change in arterial oxygen saturation, and the results were imprecise (19 children; MD -1.70%, 95% CI -3.76 to 0.36). The effect of CPAP on change in arterial partial carbon dioxide pressure (pCO_2) was imprecise (2 RCTs, 50 children; MD -2.62 mmHg, 95% CI -5.29 to 0.05; low-quality evidence). Duration of hospital stay was similar in both CPAP and supportive care groups (2 RCTs, 50 children; MD 0.07 days, 95% CI -0.36 to 0.50; low-quality evidence). Two studies did not report about 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 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:
Limited, low-quality evidence suggests that breathing improved (a decreased respiratory rate) in children with bronchiolitis who received CPAP; this finding is unchanged from the 2015 review. Further evidence for this outcome was provided by the inclusion of a low-

quality study for the 2018 update. Due to the limited available evidence, the effect of CPAP in children with acute bronchiolitis is uncertain for other outcomes. Larger, adequately powered trials are needed to evaluate the effect of CPAP for children with acute bronchiolitis.

Arch Dis Child. 2019 Jan 17. pii: archdischild-2018-315846. doi: 10.1136/archdischild-2018-315846. [Epub ahead of print] (Open access available)

High-flow nasal cannula therapy for children with bronchiolitis: a systematic review and meta-analysis.

Lin J, Zhang Y, Xiong L, Liu S, Gong C, Dai J.
China

OBJECTIVES:
To review the effects and safety of high-flow nasal cannula (HFNC) for bronchiolitis.

METHODS:
Six electronic databases including PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, CQ VIP Database and Wanfang Data were searched from their inception to 1 June 2018. Randomised controlled trials (RCTs) which investigated the effects of HFNC versus other forms of oxygen therapies for bronchiolitis were included.

RESULTS:
Nine RCTs with 2121 children met the eligibility criteria. There was no significant difference in length of stay in hospital (LOS), length of oxygen supplementation (LOO), transfer to intensive care unit, incidence of intubation, respiratory rate, SpO_2 and adverse events in HFNC group compared with standard oxygen therapy (SOT) and nasal continuous positive airway pressure (nCPAP) groups. **A significant reduction of the incidence of treatment failure (risk ratio (RR) 0.50, 95% CI 0.40 to 0.62, p<0.01) was observed in HFNC group compared with SOT group, but there was a significant increase of the incidence of treatment failure (RR 1.61, 95% CI 1.06 to 2.42, p0.02) in HFNC group compared with nCPAP group.** In subgroup analysis, LOS was significantly decreased in HFNC group compared with SOT group in low-income and middle-income countries.

CONCLUSION:
The systematic review suggests HFNC is safe as an initial respiratory management, but the evidence is still lacking to show benefits for children with bronchiolitis compared with SOT or nCPAP.

Adolescent health

BMC Public Health. 2019 Jan 10;19(1):48. doi: 10.1186/s12889-018-6355-z. (Open access available)

Prevalence and correlates of psychological distress among 13-14 year old adolescent girls in North Karnataka, South India: a cross-sectional study.

Beattie TS, Prakash R, Mazzuca A, Kelly L, Javalkar P, Raghavendra T, Ramanaik S, Collumbien M, Moses S, Heise L, Isac S, Watts C.
UK, India, Canada, USA

BACKGROUND:
Mental health disorders among adolescents have emerged as a major public health issue in many low and middle-income countries, including India. There is a paucity of research on the determinants of psychological distress, particularly among the poorest girls in the poorest communities. The purpose of this study was to assess the prevalence and correlates of different indicators of psychological distress among 13-14 year old low caste girls in rural, south India.

METHODS:
Cross-sectional survey of 1191 low caste girls in two districts in north Karnataka, conducted as part of a cluster randomised-control trial. Bivariate and multivariate logistic regression analysis assessed correlates of different indicators of psychological distress.

RESULTS:
More than one third of girls (35.1%) reported having no hope for the future. 6.9% reported feeling down, depressed or hopeless in the past 2 weeks. 2.1% reported thinking they would be better off dead or of hurting themselves in some way in the past 2 weeks. 1.6% reported sexual abuse, 8.0% rrecent eve teasing and 6.3% having no parental emotional support. Suicidal ideation was independently associated with sexual abuse (AOR 11.9 (3.0-47.0)) and a lack of parental emotional support (AOR 0.2 (0.1-0.5)). Feeling down, depressed or hopeless was independently associated with recent eve-teasing (AOR 2.9 (1.6-5.4)), a harassing or abusive school environment (AOR 3.9 (1.8-8.2)), being frequently absent (AOR 2.8 (1.5-5.5)) or having dropped out of school (AOR 2.1 (1.0-4.3)), and living in Vijayapura district (AOR 2.5 (1.6-4.1)). Having no hope for the future was independently associated with a range of factors, including recent "eve-teasing" (AOR 1.5 (1.0-2.4)), being engaged (AOR 2.9 (0.9-9.7)), not participating in groups (AOR 0.5 (0.4-0.6)) and a lack of emotional support (AOR 0.6 (0.4-0.7)).

CONCLUSIONS:
Rather than being a time of optimism, a third of low caste girls in rural north, Karnataka have limited hope for the future, with some contemplating suicide. As well as having important development benefits, interventions that address the upstream structural and gender-norms based determinants of poor mental health, and provide adolescent services for girls who require treatment and support, should have important benefits for girls' psychological wellbeing.

BMJ Glob Health. 2018 Oct 19;3(5):e000824. doi: 10.1136/bmjgh-2018-000824. eCollection 2018. (Open access available)

Building caregivers' emotional, parental and social support skills to prevent violence against adolescent girls: findings from a cluster randomised controlled trial in Democratic Republic of Congo.

Stark L, Seff I, Asghar K, Roth D, Bakamore T, MacRae M, Fanton D'Andon C, Falb KL.
USA, France

Introduction:
Parenting programmes are increasingly popular for reducing children's exposure to interpersonal violence in low/middle-income countries, but there is limited evidence on their effectiveness. We investigated the incremental impact of adding a caregiver component to a life skills programme for adolescent girls, assessing girls' exposure to violence (sexual and others) and caregivers' gender attitudes and parenting behaviours.

Methods:
In this two-arm, single-blinded, cluster randomised controlled trial, we recruited 869 adolescent girls aged 10-14 and 764 caregivers in South Kivu, Democratic Republic of Congo. Following a baseline survey, participants were divided into 35 clusters based on age, language and location. Eighteen clusters were randomised to the treatment arm and 17 clusters to the wait-list control arm. **Adolescent girls in both arms received 32 life skills sessions; caregivers in the treatment arm received 13 complementary caregiver sessions.** The primary outcome was girls' self-reported exposure to sexual violence in the last 12 months; secondary outcomes included self-reports of specific forms of sexual violence, physical and emotional violence, transactional sex, child marriage for girls and parenting behaviours for caregivers. Intent-to-treat and per-protocol analyses were conducted.

Results:
At 12 months of follow-up, the intervention showed no impact on sexual violence (adjusted OR=0.95; 95% CI 0.65 to 1.37) or any secondary outcomes for girls. The intervention was associated with improved supportive parenting behaviours. Protocol adherence was also associated with improvements in these outcomes.

Conclusion:
While the caregiver curriculum improved some parenting outcomes, additional programmatic adaptations may be needed to reduce adolescent girls' violence exposure in humanitarian settings.

Comment
No authors from Democratic Republic of Congo

PLoS One. 2018 Aug 15;13(8):e0201362. doi: 10.1371/journal.pone.0201362. eCollection 2018. (Open access available)

Reducing violence by teachers using the preventative intervention Interaction Competencies with Children for Teachers (ICC-T): A cluster randomized controlled trial at public secondary schools in Tanzania.

Nkuba M, Hermenau K, Goessmann K, Hecker T.
Germany, Tanzania

Abstract
The high global prevalence of school violence underlines the need for prevention. However, there are few scientifically evaluated intervention approaches that aim at preventing violence by teachers. We evaluated the feasibility and efficacy of the preventative intervention **Interaction Competencies with Children for Teachers (ICC-T).** In a cluster randomized controlled trial we assessed attitudes towards and use of violence by teachers (self-reported and reported by students) at eight schools in four regions in Tanzania. Two regions were randomly assigned as intervention regions. Data were assessed in the months before and three months after intervention. In total, **158 teachers (58% females; age: 32.08 years, SD = 5.65) and 486 students (54% females; age: 15.61 years, SD = 0.89) participated in this study**. The feasibility was very good: Participants' acceptance was high and they reported a good integration of the core elements in their working routine. **The significantly stronger decrease in the use of emotional and physical violence reported both by teachers and students as well as the stronger decrease in positive attitudes of teachers towards physical and emotional violence in the intervention schools at follow-up provide initial evidence of the efficacy**. However, further evidence for the sustainability of its effect is needed.

BMJ Glob Health. 2019 May 9;4(3):e001147. doi: 10.1136/bmjgh-2018-001147. eCollection 2019.

Cost and cost-effectiveness of a parenting programme to prevent violence against adolescents in South Africa.

Redfern A, Cluver LD, Casale M, Steinert JI
Kenya, South Africa, Germany.

Introduction:
This paper presents the costs and cost-effectiveness of 'Parenting for Lifelong Health: Sinovuyo Teen', a non-commercialised parenting programme aimed at preventing violence against adolescents in low-income and middle-income countries.
Methods:
The effectiveness of Sinovuyo Teen was evaluated with a cluster randomised controlled trial in 40 villages and peri-urban townships in the Eastern Cape of South Africa from 2015 to 2016. The costs of implementation were calculated retrospectively and models of costs at scale estimated, from the perspective of the programme provider. Cost-effectiveness analysis considers both the cost per incident of abuse averted, and cost per disability-adjusted life year averted. Potential economic benefits from the societal perspective were estimated by developing a framework of possible savings.
Results:

The total implementation cost for Sinovuyo Teen over the duration of the trial was US$135 954, or US$504 per family enrolled. Among the 270 families in the treatment group, an estimated 73 incidents of physical and emotional abuse were averted (95% CI 29 to 118 incidents averted). During the trial, the total cost per incident of physical or emotional abuse averted was US$1837, which is likely to decrease to approximately US$972 if implemented at scale. By comparison, the economic benefits of averting abuse in South Africa are large with an estimated lifetime saving of US$2724 minimum per case.
Conclusion:
Parenting programmes are a cost-effective intervention to prevent the abuse of adolescents by their caregivers in South Africa, when compared with existing violence prevention programmes and cost-effectiveness thresholds based on GDP per capita.

BMC Public Health. 2018 Dec 4;18(1):1341. doi: 10.1186/s12889-018-6220-0. (Open access available)

Sexual violence among adolescent girls and young women in Malawi: a cluster-randomized controlled implementation trial of empowerment self-defense training.

Decker MR, Wood SN, Ndinda E, Yenokyan G, Sinclair J, Maksud N, Ross B, Omondi B, Ndirangu M.
USA, Malawi, Kenya, Somalia

BACKGROUND:
Globally, sexual violence is prevalent, particularly for adolescent women. This cluster-randomized controlled implementation trial examines **empowerment self-defense (ESD) for sexual assault risk reduction among school-age women in Malawi**.

METHODS:
The unit of randomization and analysis was the school (n = 141). Intervention participants received a 12-h intervention over 6 weeks, with refreshers. **Primary outcomes were past-year prevalence and incident rate of sexual violence.** Secondary outcomes included confidence, self-defense knowledge, and, for those victimized, violence disclosure. Interaction effects on outcomes were evaluated with Poisson models with school-correlated robust variance estimates for risk ratios and incident rate ratios (baseline n = 6644, follow-up n = 4278).

RESULTS:
Past-year sexual assault prevalence was reduced among intervention students (risk ratio [RR] 0.68, 95% CI 0.56, 0.82), but not control students (interaction effect $p < 0.001$). Significant increases in self-defense knowledge were observed solely among intervention students (RR 3.33, 95% CI 2.76, 4.02; interaction effect $p < 0.001$). Significant changes in sexual violence prevalence and knowledge were observed for both primary and secondary students. Favorable reductions were also observed in sexual violence incident rate among students overall (interaction effect $p = 0.01$).

CONCLUSIONS:
This intervention reduced sexual violence victimization in both primary and secondary school settings. Results support the effectiveness of ESD to address sexual violence, and approach the elimination of violence against women and girls set forth with Sustainable Development Goal #5. Implementation within the education system can enable sustainability and reach.

JAMA Netw Open. 2018 Aug 3;1(4):e181213. doi: 10.1001/jamanetworkopen.2018.1213. (Open access available)

Effect of a Behavioral Intervention on Perpetrating and Experiencing Forced Sex Among South African Adolescents: A Secondary Analysis of a Cluster Randomized Trial.

Jemmott JB 3rd, O'Leary A, Jemmott LS, Ngwane ZP, Teitelman AM, Makiwane MB, Bellamy SL.
USA, South Africa

Importance:
Scant research has investigated interventions to reduce forced sexual intercourse among adolescents. The need for such interventions is especially great in South Africa, which has some of the highest rates of sexual assault in the world.

Objectives:
To determine whether an HIV/sexually transmitted disease risk-reduction intervention that reduced sexual risk behavior and sexually transmitted disease prevalence also reduced the perpetration and experience of forced sex among South African adolescents.

Design, Setting, and Participants:
A cluster randomized clinical trial, at schools located in a township and a semirural area, Eastern Cape Province, South Africa. Matched pairs of schools were randomly selected (9 of 17); of 1118 students in sixth grade at these 18 schools who had parent or guardian consent, 1057 (94%) were enrolled, and those not reporting forced sex perpetration before the intervention were included in the analyses (n = 1052). Post hoc secondary analysis of a cluster randomized clinical trial was performed, with baseline and 3-, 6-, 12-, 42-, and 54-month postintervention assessments between October 4, 2004, and June 30, 2010. Generalized estimating equation Poisson regression analyses adjusting for gender and clustering within schools were conducted between August 23, 2017, and April 30, 2018. Recruiters and data collectors, but not intervention facilitators, were blind to the participants' intervention assignment.

Interventions:
Theory-based, culturally adapted, 6-session HIV/sexually transmitted disease risk-reduction intervention (Let Us Protect Our Future intervention) and attention-matched, chronic

disease prevention control intervention implemented by specially trained man and woman cofacilitators from the community.

Main Outcomes and Measures:
Study outcomes for this secondary analysis (planned after the data were collected) are self-reports of perpetrating and experiencing forced vaginal intercourse.

Results:
Participants included 1052 adolescents (557 girls [53%]; mean [SD] age, 12.4 [1.2] years) reporting not perpetrating forced sex at baseline. Fewer intervention than control participants reported forced sex perpetration postintervention compared with the control group at 3 months (9 of 561 [2%] vs 20 of 491 [4%]; risk ratio [RR], 0.978; 95% CI, 0.959-0.997), 6 months (17 of 561 [3%] vs 35 of 491 [7%]; RR, 0.964; 95% CI, 0.941-0.988), 12 months (21 of 561 [4%] vs 42 of 491 [9%]; RR, 0.959; 95% CI, 0.934-0.985), 42 months (41 of 561 [7%] vs 56 of 491 [11%]; RR, 0.967; 95% CI, 0.937-0.998), and 54 months (52 of 561 [9%] vs 68 of 491 [14%]; RR, 0.964; 95% CI, 0.932-0.997).

Conclusions and Relevance:
In settings with high rates of sexual assault, the use of theory-based culturally adapted interventions with early adolescents may reduce rates of perpetrating and experiencing forced sex.

Reprod Health. 2018 Aug 17;15(1):139. doi: 10.1186/s12978-018-0582-8. (Open access available)

Use of menstrual cups among school girls: longitudinal observations nested in a randomised controlled feasibility study in rural western Kenya.

van Eijk AM, Laserson KF, Nyothach E, Oruko K, Omoto J, Mason L, Alexander K, Oduor C, Mohammed A, Eleveld A, Ngere I, Obor D, Vulule J, Phillips-Howard PA.
UK, Kenya, USA

BACKGROUND:
A menstrual cup can be a good solution for menstrual hygiene management in economically challenged settings. As part of a pilot study we assessed uptake and maintenance of cup use among young school girls in Kenya.

METHODS:
A total of 192 girls between 14 to 16 years were enrolled in 10 schools in Nyanza Province, Western Kenya; these schools were assigned menstrual cups as part of the cluster-randomized pilot study. Girls were provided with menstrual cups in addition to training and guidance on use, puberty education, and instructions for menstrual hygiene. During repeated individual visits with nurses, girls reported use of the menstrual cup and nurses recorded colour change of the cup.

RESULTS:

Girls were able to keep their cups in good condition, with only 12 cups (6.3%) lost (dropped in toilet, lost or destroyed). Verbally reported cup use increased from 84% in the first 3 months (n = 143) to 96% after 9 months (n = 74). Colour change of the cup, as 'uptake' indicator of use, was detected in 70.8% of 192 participants, with a median time of 5 months (range 1-14 months). Uptake differed by school and was significantly higher among girls who experienced menarche within the past year (adjusted risk ratio 1.29, 95% CI 1.04-1.60), and was faster among girls enrolled in the second study year (hazard ratio 3.93, 95% CI 2.09-7.38). The kappa score comparing self-report and cup colour observation was 0.044 (p = 0.028), indicating that agreement was only slightly higher than by random chance.

CONCLUSIONS:
Objective evidence through cup colour change suggests school girls in rural Africa can use menstrual cups, with uptake improving with peer group education and over time.

AIDS Behav. 2019 Jan;23(1):91-104. doi: 10.1007/s10461-018-2249-4.

Effects of a School-Based Intervention on Frequency and Quality of Adolescent-Parent/Caregiver Sexuality Communication: Results from a Randomized-Controlled Trial in Uganda.

Katahoire AR, Banura C, Muhwezi WW, Bastien S, Wubs A, Klepp KI, Aarø LE.
Uganda, Canada, Norway

Abstract
In a cluster-randomized trial conducted in 22 government secondary schools in Uganda, effects of a school-based intervention aimed at improving aspects of parent/caregiver-adolescent communication on sexuality were examined. The intervention comprised classroom-based education sessions, take home assignments for students to discuss with parents/caregivers and parenting workshops. Baseline and post intervention questionnaires were completed by students and by parents/caregivers. Effect estimates were significant for both students and parents/caregivers on sexuality communication frequency and quality, and for positive and negative attitudes towards sex-related communication, all in the desired direction with effect sizes ranging from 0.17 to 0.38. Effects on four sum scores related to general parenting proved significant only for parents'/caregivers' legitimacy with regard to rule setting (parents'/caregivers' reports only). These results suggest that in Uganda, using schools as gateways, parent/caregiver-adolescent communication can be improved through modification of existing school curricula, training teachers in learner-centred approaches and through mobilization and training of parents/caregivers.

J Adolesc Health. 2019 Jun 18. pii: S1054-139X(19)30165-X. doi: 10.1016/j.jadohealth.2019.03.007

Promoting Gender Egalitarian Norms and Practices Among Boys in Rural India: The Relative Effect of Intervening in Early and Late Adolescence.

Gupta AK, Santhya KG.

India.
PURPOSE:
Although the importance of exposing adolescent boys to gender transformative programs has been recognized, such programs are limited in India. Studies that assessed the relative effect of intervening in early compared with late adolescence are even more limited. This article examines the differential effect of exposing boys to a gender transformative program in early and late adolescence on their gender role attitudes and practices.
METHODS:
We used data from a cluster randomized trial of a gender transformative life-skills education cum sports-coaching program for younger boys (aged 13-14 years) and older boys (aged 15-19 years) (N = 962) and used generalized estimating equation model to examine the differential effect.
RESULTS:
The intervention had a greater effect in helping younger than older boys to espouse gender-egalitarian attitudes (β = .669; p < .001 vs. β = .344; p < .001) and attitudes rejecting men's controlling behaviors (β = .973; p < .003 vs. β = .453; p < .088), men's perpetration of wife beating (β = .423; p < .002 vs. β = .282; p < .035), and violence on unmarried girls (β = .332; p < .038 vs. β = .306; p < .045). Younger boys had higher odds of reporting that their peers would respect them for acting in gender-equitable ways (odds ratio [OR] = 2.15; p < .003) compared with older boys (OR = 1.78; p < .014). However, younger boys had lower odds of intervening to stop incidents of violence that they had witnessed, compared with older boys (OR = 2.17; p < .03 vs. OR = 2.56; p < .002). These differences remained significant even when difference in regular exposure to the intervention was adjusted.
CONCLUSIONS:
Gender transformative programs are likely to be more effective in changing traditional attitudes and practices among boys if they target them during early adolescence compared with late adolescence.

Int J Environ Res Public Health. 2018 Aug 26;15(9). pii: E1839. doi: 10.3390/ijerph15091839. (Open access available)

A Randomized Controlled Trial of a Theory-Informed School-Based Intervention to Prevent Waterpipe Tobacco Smoking: Changes in Knowledge, Attitude, and Behaviors in 6th and 7th Graders in Lebanon.

Nakkash R, Lotfi T, Bteddini D, Haddad P, Najm H, Jbara L, Alaouie H, Al Aridi L, Al Mulla A, Mahfoud Z, Afifi RA.
Lebanon, Germany, UAE, USA

Abstract
Waterpipe tobacco smoking (WTS) is spreading worldwide. Research has indicated health consequences of WTS similar to cigarettes. Prevalence of WTS is high among young people. In Lebanon, current use rates of 35% have been documented among 13⁻15 year olds. We evaluated a school-based intervention. *Method*: We conducted a randomized-controlled-trial of a theory-informed WTS intervention. The intervention consisted of ten sessions based on

social cognitive theory and the social influences approach. Thirty-one schools participated: 14 intervention and 17 control; a total of 1279 students completed pre and post assessments. We measured knowledge, attitudes and self-reported behaviors related to WTS using Chi-square tests and regression analyses to compare results between the two study arms. *Results*: **The intervention increased knowledge of intervention group compared to control group participants-about WTS constituents and health consequences; and shifted attitudes of intervention group participants to be even more unfavorable towards WTS. We found no impact of the intervention on WTS behaviors**. *Discussion*: The effectiveness of the intervention on knowledge and attitudes supports previous research. The lack of intervention effect on behavior is not surprising given the timing of the post assessment immediately after the intervention, and the social context that was supportive of waterpipe use.

PLoS One. 2019 Jan 23;14(1):e0210468. doi: 10.1371/journal.pone.0210468. eCollection 2019. (Open access available)

Peer-facilitated community-based interventions for adolescent health in low- and middle-income countries: A systematic review.

Rose-Clarke K, Bentley A, Marston C, Prost A.
UK

BACKGROUND:
Adolescents aged 10-19 represent one sixth of the world's population and have a high burden of morbidity, particularly in low-resource settings. We know little about the potential of community-based peer facilitators to improve adolescent health in such contexts.

METHODS:
We did a systematic review of peer-facilitated community-based interventions for adolescent health in low- and middle-income countries (LMICs). We searched databases for randomised controlled trials of interventions featuring peer education, counselling, activism, and/or outreach facilitated by young people aged 10-24. We included trials with outcomes across key areas of adolescent health: infectious and vaccine preventable diseases, undernutrition, HIV/AIDS, sexual and reproductive health, unintentional injuries, violence, physical disorders, mental disorders and substance use. We summarised evidence from these trials narratively. PROSPERO registration: CRD42016039190.

RESULTS:
We found 20 studies (61,014 adolescents). Fourteen studies tested interventions linked to schools or colleges, and 12 had non-peer-facilitated components, e.g. health worker training. Four studies had HIV-related outcomes, but none reported reductions in HIV prevalence or incidence. Nine studies had clinical sexual and reproductive health outcomes, but only one reported a positive effect: a reduction in Herpes Simplex Virus-2 incidence. Three studies had violence-related outcomes, two of which reported reductions in physical violence by school staff and perpetration of physical violence by adolescents. Seven studies had mental health

outcomes, four of which reported reductions in depressive symptoms. Finally, we found eight studies on substance use, four of which reported reductions in alcohol consumption and smoking or tobacco use. There were no studies on infectious and vaccine preventable diseases, undernutrition, or injuries.

CONCLUSIONS:
There are few trials on the effects of peer-facilitated community-based interventions for adolescent health in LMICs. Existing trials have mixed results, with the most promising evidence supporting work with peer facilitators to improve adolescent mental health and reduce substance use and violence.

Adolesc Health Med Ther. 2019 Mar 28;10:39-47. doi: 10.2147/AHMT.S181001. eCollection 2019. (Open access available)

Attitudes and perceived barriers toward healthy lifestyle behaviors in Jordanian adolescents: a developing country perspective.

Al-Sheyab NA, Alomari MA, Hayajneh AA, Shah S.
Jordan

BACKGROUND AND AIMS:
There is an urgent need to address the role of healthy diet and behaviors promoting health among school adolescents in order to tailor appropriate interventions in Jordanian schools. This study aims to evaluate the reliability and validity of the Arabic version of Students As LifeStyle Activists (SALSA) survey alongside Jordanian adolescents' attitudes and perceived barriers to healthy eating and physical activity.

METHODS:
This study uses baseline data from a randomized controlled trial recruiting school students from 29 male and 27 female public high schools that have grades 7 and 8. Cronbach's alpha and principal components analysis/factor analysis were used to check reliability and validity. Numbers, percentages, and chi square were used to explore healthy diet and physical activities preferences among Jordanian school students and determine gender differences for all evaluated items.

RESULTS:
The Arabic version-SALSA survey has acceptable Cronbach's alpha values (>0.78) for most of its scales. Five scales were derived from the Arabic version-SALSA survey using principal components analysis/factor analysis (factors loading above 0.3). A higher proportion of female students agreed that "healthy food makes you more comfortable" compared to male students (44% vs 36%, $P<0.05$). Few Jordanian high school students held positive attitudes toward healthy food. This study identified both social and personal barriers to exercise among Jordanian adolescents, including lack of skills for physical activity, easy access and low cost of fast food, scarce opportunities for physical activity, and lack of peers and friends.

CONCLUSION:
Interventions should be tailored to health attitudes and beliefs of Jordanian school students in parallel with improving physical resources and enhancing peer and/or friend support.

J Adolesc Health. 2019 Apr 23. pii: S1054-139X(19)30069-2. doi: 10.1016/j.jadohealth.2019.01.027. [Epub ahead of print]

Intervention Increases Physical Activity and Healthful Diet Among South African Adolescents Over 54 Months: A Randomized Controlled Trial.

Jemmott JB 3rd, Zhang J, Jemmott LS, Icard LD, Ngwane Z, Makiwane M, O'Leary A.
South Africa

PURPOSE:
Scant research has investigated whether health promotion interventions have sustained effects in increasing physical activity and healthful diet among adolescents in sub-Saharan Africa, which is experiencing an epidemiological transition from infectious diseases to noncommunicable diseases as leading causes of mortality. We examined whether an intervention increased adherence to 5-a-day diet and physical activity guidelines during a 54-month postintervention period among South African adolescents and whether its effects weakened at long-term (42 and 54 months postintervention) compared with short-term (3, 6, and 12 months postintervention) follow-up.

METHODS:
We randomized 18 randomly selected schools serving grade 6 learners (mean age = 12.6) in a township and a semirural area in Eastern Cape Province, South Africa, to one of the two 12-hour interventions: health promotion, targeting healthful diet and physical activity; attention-matched control, targeting sexual risk behaviors. We tested the intervention's effects on adherence to 5-a-day diet and physical activity guidelines using generalized estimating equations logistic regression models adjusting for baseline behavior and clustering within schools.

RESULTS:
Health promotion intervention participants had higher odds of meeting 5-a-day diet and physical activity guidelines than control participants. The effect on 5-a-day diet did not weaken at long-term compared with short-term follow-up, but the effect on physical activity guidelines was weaker at long-term follow-up, mainly because of a reduced effect on muscle-strengthening physical activity. The intervention also increased health promotion attitude and intention and health knowledge and reduced binge drinking compared with the control group.
CONCLUSIONS:
A 12-hour intervention in grade 6 shows promise in increasing self-reported adherence to healthful diet and physical activity guidelines during a 4.5-year postintervention period among South African adolescents.

Adolescents and HIV prevention and treatment

BMC Public Health. 2019 Jan 28;19(1):117. doi: 10.1186/s12889-019-6447-4. (Open access available)

Effectiveness of community adolescent treatment supporters (CATS) interventions in improving linkage and retention in care, adherence to ART and psychosocial well-being: a randomised trial among adolescents living with HIV in rural Zimbabwe.

Willis N, Milanzi A, Mawodzeke M, Dziwa C, Armstrong A, Yekeye I, Mtshali P, James V.
Zimbabwe, South Africa

BACKGROUND:
Engagement with community adolescent treatment supporters (CATS) improves adherence, psychosocial well-being, linkage and retention in care among adolescents living with HIV. However, there is an urgent need for empirical evidence of the effectiveness of this approach, in order to inform further programmatic development, national and international policy, guidelines and service delivery for adolescents living with HIV. This study set out to determine the effectiveness of CATS services on improving linkage to services and retention in care, adherence and psychosocial well-being among adolescents living with HIV in Zimbabwe.

METHODS:
A randomised trial was conducted in Gokwe South district, Zimbabwe over a period of 12 months. Ninety-four HIV-positive adolescents, 10-15 years old, on antiretroviral therapy were recruited to the study. 47 participants received standard of care from the Ministry of Health and Child Care and 47 received the same standard of care plus CATS services. Data collection involved a questionnaire which was administered at baseline then repeated at three, six, nine and twelve months for all participants. Survey questions on confidence, self-esteem and self-worth had a three-point Likert scale. Stigma, quality of life and the linkages to services and retention questions had a five-point Likert scale.

RESULTS:
Survey questionnaires were completed with response rates of 40 out of 47 (85%) for the intervention arm, and 28 out of 47 (60%) for the control arm, at end-line. **The intervention group were 3.9 times more likely to adhere to treatment compared to the control group**. Linkage to services and retention in care within the intervention group increased compared with a decrease in the control arm. The intervention group reported a statistically significant increase in confidence, self-esteem, self-worth ($p < 0.001$) and quality of life compared ($p = 0.028$) with a decrease in the control arm.

CONCLUSIONS:

This study found that adolescents receiving the CATS service had improved linkage to services and retention in care, improved adherence and improved psychosocial well-being compared to adolescents who did not have access to such services.

AIDS Behav. 2019 Apr 30. doi: 10.1007/s10461-019-02518-4. [Epub ahead of print]

Gender Differences in HIV/HSV-2: Evidence from a School Support Randomized Controlled Trial Among Orphaned Adolescents in Kenya.

Cho H, Deming ME, Park JH, Iritani B.
Kenya

Women and girls are disproportionately affected by HIV and other sexually transmitted infections (STIs) such as Herpes Simplex Virus type-2 (HSV-2) in Sub-Saharan Africa (SSA). Given this gender disparity and women's vulnerability to HIV/STIs, prevention efforts often target women, but relatively little attention has been paid to compare whether HIV interventions produce equal program effects across gender. **The purpose of this study is to examine whether the school support intervention had equal program effects on study outcomes and biomarkers by gender among orphaned adolescents in Kenya**.
A randomized controlled trial was conducted to test whether keeping orphaned boys and girls in school reduced risky sexual behaviors and prevented HIV/HSV-2 infection in Kenya (N = 835). We collected four annual surveys and biomarkers measures of HIV and HSV-2 at Time 1 and Time 4. Regression analysis and multi-level linear mixed models were conducted, and t test with Satterthwaites' method for each regression coefficients was used to compare program effects by gender. There were substantial gender differences on risky sexual behaviors, HSV-2 infection, and gendered ideologies prior to intervention implementation. The school support intervention had significant gender-specific program impacts on HSV-2**. The intervention females experienced a 36% increase in HSV-2 infection while intervention males experienced a 23% decrease after 3 years of program implementation.** Differential program effects by gender on attitudes toward abstaining from sex were also found. More scientific research is needed to test whether HIV interventions produce equal program impacts by gender. Prevention programs should recognize gender-specific program effects and address individual, relational, and contextural factor that reinforce the gender disparity in HIV/HSV-2 risk.

JMIR Mhealth Uhealth. 2018 Aug 1;6(8):e10482. doi: 10.2196/10482.

A Smartphone Game-Based Intervention (Tumaini) to Prevent HIV Among Young Africans: Pilot Randomized Controlled Trial.

Winskell K, Sabben G, Akelo V, Ondeng'e K, Obong'o C, Stephenson R, Warhol D, Mudhune V.
USA, Kenya

BACKGROUND:

There is a pressing need to ensure that youth in high HIV prevalence settings are prepared for a safer sexual debut. Smartphone ownership is increasing dramatically in low-income and middle-income countries. Smartphone games that are appropriately grounded in behavioral theory and evidence-based practice have the potential to become valuable tools in youth HIV prevention efforts in Sub-Saharan Africa.

OBJECTIVE:
To pilot-test a theory-based, empirically grounded smartphone game for young Kenyans designed to increase age and condom use at first sex, aiming to establish directionality of effects on behavior change.

METHODS:
Tumaini ("hope for the future" in Swahili) is an interactive, narrative-based game grounded in social cognitive theory. A randomized controlled pilot study was conducted in Kisumu, Western Kenya, from April to June 2017 with 60 participants aged 11-14 (mean 12.7) years. Intervention arm participants (n=30) were provided with an Android smartphone with Tumaini installed on it and were instructed to play the game for at least 1 hour a day for 16 days; control arm participants (n=30) received no intervention. All participants completed a survey on behavioral mediators, delivered via an audio computer-assisted self-interview system at baseline (T1), post intervention (T2), and at 6 weeks postintervention (T3). The postintervention survey for intervention arm participants included questions eliciting feedback on the game. Intervention arm participants and their parents participated in 8 postintervention focus group discussions. Game log files were analyzed to calculate the length of exposure to the game. Behavioral survey data were analyzed using two-sample t tests to compare mean change from T1 to T2 and to T3 for intervention versus control arm participants. Descriptive statistics on game feedback questions were computed. Focus group transcripts were uploaded to MAXQDA software, where they were labeled with deductive and inductive codes. Data were analyzed thematically and compared across demographics.

RESULTS:
Intervention arm participants played Tumaini for a mean of approximately 27 hours. The intervention arm showed significant gains in sexual health-related knowledge and self-efficacy (both P<.001), behavioral intention for risk-avoidance strategies and sexual risk communication (P=.006), and overall survey scores (P<.001) compared with the control arm at T3. The postintervention survey revealed high subjective measures of the game's value, relevance, and appeal. Focus groups identified a wide range of knowledge and skills the participants had gained, including setting goals and planning how to achieve them, which was perceived as a key motivator for avoiding or reducing risk.

CONCLUSIONS:
The study supports the need for further research to assess the efficacy of the game-based intervention. If proven efficacious, smartphone games have the potential to dramatically increase the reach of culturally adapted behavioral interventions while ensuring fidelity to intervention design.

Adolesc Health Med Ther. 2018 Dec 4;9:211-235. doi: 10.2147/AHMT.S153204. eCollection 2018. (Open access available)

Screening for HIV and linkage to care in adolescents: insights from a systematic review of recent interventions in high- versus low- and middle-income settings.

Zanoni BC, Elliott RJ, Neilan AM, Haberer JE.
USA

Introduction:
Compared to adults, adolescents and young adults have a higher incidence of HIV infection, yet lower rates of HIV testing. Few evidence-based interventions effectively diagnose new HIV infections among adolescents while successfully providing linkage to care.

Methods:
We conducted a systematic review of recent interventions to increase HIV testing among adolescents and young adults using data retrieved from PubMed and Google Scholar, and using abstracts presented at the International AIDS Society conferences and Conference on Retroviruses and Opportunistic Infections published between January 1, 2015, and April 28, 2018.

Results:
We identified 36 interventions (N=14 in high- income countries and N=22 in low- and middle-income countries) that were published in the literature (N=28) or presented at conferences (N=8). Interventions were categorized as behavioral/educational, alternate venue/self-testing, youth-friendly services, technology/mobile health, incentives, or peer-based/community-based interventions. The studies consisted of randomized controlled trials (RCTs), prospective and retrospective observational studies, and quasi-experimental/pre-post evaluations with variable sample sizes. Study designs, populations, and settings varied. All categories showed some degree of acceptability, yet not all interventions were effective in increasing HIV testing. Effectiveness was seen in more than one RCT involving technology/mobile health (2/3 RCTs) and alternative venue/self-testing (3/3 RCTs) interventions, and only in one RCT each for behavioral interventions, community interventions, and incentives. There were no effective RCTs for adolescent-friendly services. Data were limited on the number of new infections identified and on the methods to increase linkage to care after diagnosis.
Conclusion:
Future studies should include combinations of proven methods for engaging adolescents in HIV testing, while ensuring effective methods of linkage to care.

AIDS. 2019 Jan 27;33(1):83-91. doi: 10.1097/QAD.0000000000002037.

Age-disparate partnerships and incident HIV infection in adolescent girls and young women in rural South Africa.

Stoner MCD, Nguyen N, Kilburn K, Gómez-Olivé FX, Edwards JK, Selin A, Hughes JP, Agyei Y, Macphail C, Kahn K, Pettifor A.
USA, Ghana, Austyralia, South Africa, Sweden

OBJECTIVE:
Adolescent girls and young women (AGYW) have a much higher risk of HIV infection than young men of the same age. One hypothesis for this disparity is AGYW are more likely to be in sexual partnerships with older men with HIV; however, evidence has been inconclusive.

DESIGN:
We used longitudinal data from a randomized trial in South Africa (HPTN 068) to determined whether partner age difference is associated with incident HIV infection in AGYW.

METHODS:
Age difference was examined continuously and dichotomously (≥5 years). We examined inverse probability of exposure weighted survival curves and calculated time-specific risk differences and risk ratios over 5.5 years of follow-up. We also used a marginal structural Cox model to estimate hazard ratios over the entire study period.

RESULTS:
Risk of HIV was higher in AGYW with an age-disparate partnership versus not and the risk difference was largest at later time points. At 5.5 years, AGYW with an age-disparate partnership had a 12.6% (95% confidence interval 1.9-23.3) higher risk than AGYW with no age-disparate partnerships. The weighted hazard ratio was 1.91 (95% confidence interval 1.33-2.74), an association that remained after weighting for either transactional or condomless sex, and after examining continuous age-differences.

CONCLUSION:
Age-disparate partnerships increased risk of HIV infection, even after accounting for transactional sex and condomless sex. The relationship between age-disparate partnerships and HIV infection may be explained by increased exposure to infection from men in a higher HIV prevalence pool rather than differences in sexual behaviour within these partnerships.

Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

Proc Nutr Soc. 2019 May;78(2):197-207. doi: 10.1017/S0029665118002847. Epub 2019 Jan 30.
(Open access available)

Iron biofortification interventions to improve iron status and functional outcomes.

Finkelstein JL, Fothergill A, Hackl LS, Haas JD, Mehta S.
USA

This analysis was conducted to evaluate the evidence of the efficacy of iron biofortification interventions on iron status and functional outcomes. Iron deficiency is a major public health problem worldwide, with a disproportionate impact on women and young children, particularly those living in resource-limited settings. Biofortification, or the enhancing of micronutrient content in staple crops, is a promising and sustainable agriculture-based approach to improve nutritional status. Previous randomised efficacy trials and meta-analyses have demonstrated that iron-biofortification interventions improved iron biomarkers; however, no systematic reviews to date have examined the efficacy of biofortification interventions on health outcomes. **We conducted a systematic review of the efficacy of iron-biofortified staple crops on iron status and functional outcomes: cognitive function (e.g. attention, memory) and physical performance.** Five studies from three randomised efficacy trials (i.e. rice, pearl millet, beans) conducted in the Philippines, India and Rwanda were identified for inclusion in this review. Iron status (Hb, serum ferritin, soluble transferrin receptor, total body iron, α-1-acid glycoprotein) was measured at baseline and endline in each trial; two studies reported cognitive outcomes, and no studies reported other functional outcomes. Meta-analyses were conducted using DerSimonian and Laird random-effects methods. **Iron-biofortified crop interventions significantly improved cognitive performance in attention and memory domains, compared with conventional crops. There were no significant effects on categorical outcomes such as iron deficiency or anaemia.** Further studies are needed to determine the efficacy of iron-biofortified staple crops on human health, including additional functional outcomes and other high-risk populations.

Nutrients. 2019 Feb 12;11(2). pii: E381. doi: 10.3390/nu11020381. (Open access available)

A Randomized Feeding Trial of Iron-Biofortified Beans on School Children in Mexico.

Finkelstein JL, Mehta S, Villalpando S, Mundo-Rosas V, Luna SV, Rahn M, Shamah-Levy T, Beebe SE, Haas JD.
USA, Mexico

Iron deficiency is a major public health problem worldwide, with the highest burden among children. The objective of this randomized efficacy feeding trial was to **determine the effects of consuming iron-biofortified beans (Fe-Beans) on the iron status in children, compared to control beans (Control-Beans).** A cluster-randomized trial of biofortified beans (*Phaseolus vulgaris L*), bred to enhance iron content, was conducted over 6 months. The participants were school-aged children (*n* = 574; 5⁻12 years), attending 20 rural public boarding schools in the Mexican state of Oaxaca. Double-blind randomization was conducted at the school level; 20 schools were randomized to receive either Fe-Beans (*n* = 10 schools, *n* = 304 students) or Control-Beans (*n* = 10 schools, *n* = 366 students). School administrators, children, and research and laboratory staff were blinded to the intervention group. Iron status (hemoglobin (Hb), serum ferritin (SF), soluble transferrin receptor (sTfR), total body iron (TBI), inflammatory biomarkers C-reactive protein (CRP) and -1-acid glycoprotein (AGP)), and anthropometric indices for individuals were evaluated at the

enrollment and at the end of the trial. The hemoglobin concentrations were adjusted for altitude, and anemia was defined in accordance with age-specific World Health Organization (WHO) criteria (i.e., Hb <115 g/L for <12 years and Hb <120 g/L for 12 years). Serum ferritin concentrations were adjusted for inflammation using BRINDA methods, and iron deficiency was defined as serum ferritin at less than 15.0 µg/L. Total body iron was calculated using Cook's equation. Mixed models were used to examine the effects of Fe-Beans on hematological outcomes, compared to Control-Beans, adjusting for the baseline indicator, with school as a random effect. **An analysis was conducted in 10 schools (*n* = 269 students) in the Fe-Beans group and in 10 schools (*n* = 305 students) in the Control-Beans group that completed the follow-up. At baseline, 17.8% of the children were anemic and 11.3% were iron deficient** (15.9%, BRINDA-adjusted). A total of 6.3% of children had elevated CRP (>5.0 mg/L), and 11.6% had elevated AGP (>1.0 g/L) concentrations at baseline. **During the 104 days when feeding was monitored, the total mean individual iron intake from the study beans (Fe-bean group) was 504 mg (IQR: 352, 616) over 68 mean feeding days, and 295 mg (IQR: 197, 341) over 67 mean feeding days in the control group (*p* < 0.01).** During the cluster-randomized efficacy trial, indicators of iron status, including hemoglobin, serum ferritin, soluble transferrin receptor, and total body iron concentrations improved from the baseline to endline (6 months) in both the intervention and control groups. However, **Fe-Beans did not significantly improve the iron status indicators, compared to Control-Beans.** Similarly, there were no significant effects of Fe-Beans on dichotomous outcomes, including anemia and iron deficiency, compared to Control-Beans. **In this 6-month cluster-randomized efficacy trial of iron-biofortified beans in school children in Mexico, indicators of iron status improved in both the intervention and control groups. However, there were no significant effects of Fe-Beans on iron biomarkers, compared to Control-Beans.**

Cochrane Database Syst Rev. 2018 Dec 22;12:CD010187. doi: 10.1002/14651858.CD010187.pub2. (Open access available)

Fortification of maize flour with iron for controlling anaemia and iron deficiency in populations.

Garcia-Casal MN, Peña-Rosas JP, De-Regil LM, Gwirtz JA, Pasricha SR.
WHO, Switzerland

BACKGROUND:
Approximately 800 million women and children have anaemia, a condition thought to cause almost 9% of the global burden of years lived with disability. Around half this burden could be amenable to interventions that involve the provision of iron. Maize (corn) is one of the world's most important cereal grains and is cultivated across most of the globe. **Several programmes around the world have fortified maize flour and other maize-derived foodstuffs with iron and other vitamins and minerals to combat anaemia and iron deficiency**.
OBJECTIVES:
To assess the effects of iron fortification of maize flour, corn meal and fortified maize flour products for anaemia and iron status in the general population.

SEARCH METHODS:
We searched the following international and regional sources in December 2017 and January 2018: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; MEDLINE (R) In Process; Embase; Web of Science (both the Social Science Citation Index and the Science Citation Index); CINAHL Ebsco; POPLINE; AGRICOLA (agricola.nal.usda.gov); BIOSIS (ISI); Bibliomap and TRoPHI; IBECS; Scielo; Global Index Medicus - AFRO (includes African Index Medicus); EMRO (includes Index Medicus for the Eastern Mediterranean Region); LILACS; PAHO (Pan American Health Library); WHOLIS (WHO Library); WPRO (includes Western Pacific Region Index Medicus); IMSEAR, Index Medicus for the South-East Asian Region; IndMED, Indian medical journals; and the Native Health Research Database. We searched clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP) for any ongoing or planned studies on 17 January 2018 and contacted authors of such studies to obtain further information or eligible data if available.For assistance in identifying ongoing or unpublished studies, we also contacted relevant international organisations and agencies working in food fortification on 9 August 2016.

SELECTION CRITERIA:
We included cluster- or individually randomised controlled trials and observational studies. Interventions included (central/industrial) fortification of maize flour or corn meal with iron alone or with other vitamins and minerals and provided to individuals over 2 years of age (including pregnant and lactating women) from any country.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed the eligibility of studies for inclusion, extracted data from included studies and assessed the risk of bias of the included studies. Trial designs with a comparison group were included to assess the effects of interventions. Trial designs without a control or comparison group (uncontrolled before-and-after studies) were included for completeness but were not considered in assessments of the overall effectiveness of interventions or used to draw conclusions regarding the effects of interventions in the review.

MAIN RESULTS:
Our search yielded 4529 records. After initial screening of titles and abstracts, we reviewed the full text of 75 studies (80 records). We included 5 studies and excluded 70. All the included studies assessed the effects of providing maize products fortified with iron plus other vitamins and minerals versus unfortified maize flour. No studies compared this intervention to no intervention or looked at the relative effect of flour and products fortified with iron alone (without other vitamins and minerals). Three were randomised trials involving 2610 participants, and two were uncontrolled before-and-after studies involving 849 participants.**Only three studies contributed data for the meta-analysis and included children aged 2 to 11.9 years and women. Compared to unfortified maize flour, it is uncertain whether fortifying maize flour or corn meal with iron and other vitamins and minerals has any effect on anaemia (risk ratio (RR) 0.90, 95% confidence interval (CI) 0.58 to 1.40; 2 studies; 1027 participants; very low-certainty evidence), or on the risk of iron deficiency (RR 0.75, 95% CI 0.49 to 1.15; 2 studies; 1102 participants; very low-certainty evidence), haemoglobin concentration (mean difference (MD) 1.25 g/L, 95% CI**

-2.36 to 4.86 g/L; 3 studies; 1144 participants; very low-certainty evidence) or ferritin concentrations (MD 0.48 µg/L, 95% CI -0.37 to 1.33 µg/L; 1 study; 584 participants; very low-certainty evidence). None of the studies reported on any adverse effects. We judged the certainty of the evidence to be very low based on GRADE, so we are uncertain whether the results reflect the true effect of the intervention. We downgraded evidence due to high risk of selection bias and unclear risk of performance bias in one of two included studies, high heterogeneity and wide CIs crossing the line of no effect for anaemia prevalence and haemoglobin concentration. **It is uncertain whether fortifying maize flour with iron and other vitamins and minerals reduces the risk of anaemia or iron deficiency in children aged over 2 years or in adults.**

Curr Dev Nutr. 2019 Jun 13;3(Suppl 1). pii: nzz034.P10-099-19. doi: 10.1093/cdn/nzz034.P10-099-19. eCollection 2019 Jun. (Open access available)

A Community Trial Examining the Effectiveness of Iron-fortified Lentils to Improve Iron Status Among Bangladeshi Adolescent Girls: Results from a Baseline Survey (P10-099-19)

Yunus F, Das A, Jalal C, Afsana K, Podder R, Vandenberg A, Henry C, DellaValle D
USA, Bangladesh

Objectives:
Despite all efforts, iron deficiency (ID) and iron deficiency anaemia (IDA) among adolescent girls remains a public health concern for Bangladesh. The objective of the current analysis was to examine baseline data from an effectiveness trial with the aim to compare prevalence of anemia, ID and IDA with Bangladesh's National Micronutrients Status Survey 2011-12.
Methods:
A community-based, double-blind, cluster randomized controlled trial is being conducted among n = 1260 Bangladeshi adolescent girls (10-17 years). Treatment groups include: 1) Fe-fortified lentils; 2) unfortified lentils and 3) usual intake (no intervention). Within the lentil groups, participants are being served 250 g cooked lentils with half a cup of cooked rice 5 days/week for 85 feeding days. All Fe-fortification and processing of lentils were carried out at the University of Saskatchewan. Anemia, ID and IDA were defined according to WHO (2011) cut-off values.
Results:
At baseline, age of participants was 13.5 ± 2.0 years; BMI 18.2 ± 3.0 kg/m2 (or 38th percentile BMI-for-age); hemoglobin 12.4 ± 1.1 g/dL, serum ferritin 54.2 ± 36.3 ng/mL, sTfR 3.7 ± 2.6 µg/mL, and CRP 1.2 ± 3.9 mg/L. 26.6% girls were clinically anemic (non-pregnant-Hb <12 g/dl), 19.9% of those were mildly anemic (non-pregnant-Hb: 11-11.9 g/dl), 5.9% were moderately anemic (non-pregnant-Hb: 8.0-10.9 g/dl) anemic, and 0.8% were severely anemic (<8.0 g/dL). We found 9.2% of girls were ID (serum ferritin <15 µg/l).
Conclusions:
One-fourth of rural Bangladeshi adolescent girls were anemic, and one-tenth were ID. This shows that rural anemia prevalence has increased ~8.5% (26.6% vs 18.1%), ID has slightly increased (9.2% vs 10.0%) and IDA has increased (6.1% vs 1.8%) over the 7 years since the Bangladesh National Micronutrients Status Survey 2011-12. We can conclude from these

baseline data that Bangladesh has made poor progress in reducing adolescent girls' anemia with public policy efforts.

Anaesthesia and intensive care

(see also Asthma)

Pediatr Anaesth. 2019 Apr;29(4):304-309. doi: 10.1111/pan.13582. Epub 2019 Jan 24. (Open access available)

Comparison of low-fresh gas flow technique to standard technique of sevoflurane induction in children-A randomized controlled trial.

Singh A, Sinha R, Aravindan A, Kumar KR, Datta PK.
India

BACKGROUND:
Although sevoflurane is preferred for inhalational induction in children, financial and environmental costs remain major limitations. The aim of this study was to determine if the use of low-fresh gas flow during inhalational induction with sevoflurane could significantly reduce agent consumption, without adversely affecting induction conditions.

METHODS:
After institutional ethical committee approval, 50 children, aged 1-5 years, undergoing ophthalmic procedures under general anesthesia, were randomized into two groups-standard induction (Group S) and low-flow induction (Group L). **A pediatric circle system with 1 L reservoir bag was primed with 8% sevoflurane in oxygen at 6 L min for 30 seconds before beginning induction. In Group S, fresh gas flow was maintained at 6 L min until the end of induction. In Group L, fresh gas flow was reduced to 1 L min after applying facemask (time = T0).** In both groups, sevoflurane was reduced to 5% after loss of eyelash reflex (T1). Once adequate depth of anesthesia was achieved (regular respiration, loss of muscle tone, and absence of movement to trapezius squeeze), intravenous access was secured (T2), followed by insertion of an appropriately sized LMA-Classic™ (T3). Heart rate and endtidal sevoflurane concentration were measured at each of the above time points, and at 15 seconds following laryngeal mask airway insertion (T4). The total amount of sevoflurane consumed during induction was recorded.

RESULTS:
Sevoflurane consumption was significantly lower in Group L (4.17 ± 0.70 mL) compared to Group S (8.96 ± 1.11 mL) (mean difference 4.79 [95% CI = 4.25-5.33] mL; P < 0.001). Time to successful laryngeal mask airway insertion was similar in both groups. There were no significant differences in heart rate, incidence of reflex tachycardia, or need for rescue propofol.

CONCLUSION:

Induction of anesthesia with sevoflurane using low-fresh gas flow is effective in reducing sevoflurane consumption, without compromising induction time and conditions.

Anesth Analg. 2018 Aug 29. doi: 10.1213/ANE.0000000000003717. [Epub ahead of print]

Incentive-Based Game for Allaying Preoperative Anxiety in Children: A Prospective, Randomized Trial.

Chaurasia B, Jain D, Mehta S, Gandhi K, Mathew PJ.
India

BACKGROUND:
Induction of anesthesia can be distressing both for children and their parents. Nonpharmacological behavioral interventions can reduce the anxiety of children without significant adverse effects as seen with sedative medications. We hypothesized that the use of **incentive-based game therapy in conjunction with parental involvement would be a simple and cost-effective intervention in reducing the preoperative anxiety in children**.

METHODS:
Eighty children between the age group of 4 and 8 years scheduled to undergo surgery were randomly assigned to a control group (n = 40) and intervention group (n = 40). Children in the intervention group participated in an incentive-based game in the preoperative room. Anesthesia was induced with parental presence in both the groups. The modified Yale Preoperative Anxiety Scale (mYPAS) score to measure the anxiety of the children during induction was taken as the primary outcome. Induction Compliance Checklist score and parental satisfaction were assessed as secondary outcomes.

RESULTS:
The mYPAS score of children in the intervention group was significantly less than the control group during anesthesia induction. The mean difference (95% confidence interval [CI]) of the mYPAS at induction between the 2 groups was 20 (95% CI, 16-24; P < .001). Fourteen (35%) children in the intervention group and 2 (5%) children in control group displayed no anxiety (mYPAS score <30) (difference of -30%; 95% CI, -11% to -49%; P < .001). Children in the intervention group were more compliant with mask induction and had a significantly less Induction Compliance Checklist score compared to the control (P < .001). Thirty (75%) parents in the intervention group were satisfied at the end of surgery compared to 6 (15%) in the control group (difference of -60%; 95% CI, -39% to -73%; P < .001).

CONCLUSIONS:
The use of incentive-based game therapy reduces the anxiety scores during induction of anesthesia and improves the compliance to facemask induction in children undergoing surgery. It can form a simple, cost-effective, and easy-to-administer technique that can be easily applied in low-income settings.

J Anaesthesiol Clin Pharmacol. 2019 Jan-Mar;35(1):65-69. doi: 10.4103/joacp.JOACP_73_18.
(Open access available)

Comparative evaluation of the efficacy of two anesthetic gels (2% lignocaine and 20% benzocaine) in reducing pain during administration of local anesthesia - A randomized controlled trial.

Nair M, Gurunathan D.
India

BACKGROUND AND AIMS:
Topical anesthetic agents are widely used in the field of pediatric dentistry to reduce pain and apprehension during administration of local anesthesia. Various topical anesthetic agents are available, among which the most commonly used ones are lignocaine and benzocaine. Hence we planned this study to compare and evaluate the effectiveness of topical anesthesia on needle insertion pain during administration of inferior alveolar nerve block.

MATERIAL AND METHODS:
This double blind clinical study included 30 children of 4-8 years of age who were divided equally into two groups: Group A-2% lignocaine hydrochloride gel (Lox 2%) and Group B-20% benzocaine gel (ProGel-B). The intervention involved assessment of pain perception by the child during administration of inferior alveolar nerve block. The child's pain assessment was done using modified Wong-Baker pain rating scale. The ratings were subjected to statistical analysis.

RESULTS:
In Group A, 6.7% (*N* = 1) showed slight pain, 66.7% (*N* = 10) showed moderate pain, and 26.7% (*N* = 4) showed severe pain. In Group B, 46.7% (*N* = 7) showed no pain, 46% (*N* = 7) showed slight pain, and 6.7% (*N* = 1) showed moderate pain on needle insertion. (*P* value -0.000).

CONCLUSION:
This study demonstrates that there is a highly significant difference between the topical anesthetic effectiveness of 2% lignocaine and 20% benzocaine on needle insertion pain in inferior alveolar nerve block. **Twenty percent benzocaine showed better results than 2% lignocaine in reducing the needle insertion pain**.

J Anaesthesiol Clin Pharmacol. 2019 Jan-Mar;35(1):25-29. doi: 10.4103/joacp.JOACP_118_18.
(Open access available)

Comparative evaluation of Truview evo2 and Macintosh laryngoscope for ease of orotracheal intubation in children - A prospective randomized controlled trial.

Pangasa N, Dali JS, Sharma KR, Arya M, Pachisia AV.
India

BACKGROUND AND AIMS:
Truview evo2 has been found to improve the glottic view when compared with the Miller blade in pediatric population. However, there is limited literature comparing it with Macintosh laryngoscope in children. **We thus aimed to assess and compare Truview evo2 with the Macintosh laryngoscope for orotracheal intubation in children with regards to time to intubate, laryngoscopic view, ease of intubation, and associated hemodynamic changes**.

MATERIAL AND METHODS:
Fifty ASA I-II children aged 2-8 years for elective surgery requiring general anesthesia with orotracheal intubation participated in this prospective randomized-controlled study. They were randomly allocated to two groups. In group-M (*N* = 25), laryngoscopy and intubation were performed using Macintosh laryngoscope, and in group-T (*N* = 25), Truview evo2 laryngoscope was used. Modified Cormack-Lehane grade, time to intubation, intubation difficulty score (IDS), and hemodynamic changes were compared between the groups. Data were analyzed using SPSS statistical software version 17 and *P* value <0.05 was considered statistically significant.

RESULTS:
CL grade 1 was found in a larger number of patients of group-T (*P* = 0.003) and CL grades2a and 2b were found in a larger number of patients of group-M (*P* = 0.023 and *P* = 0.037, respectively). The mean time to intubation was significantly longer in group-T (19.0 ± 3.4 seconds) than in group-M (13.1 ± 2.1 seconds), *P* = 0.00. The over all IDS was lower in group-T than group M [i.e. median (IQR): 0 (0-0) vs 1 (0-2), respectively]. Heart rate, systolic and diastolic blood pressure, and oxygen saturation were comparable between the groups at all times.

CONCLUSION:
Truview evo2 provides better laryngeal view and has a lesser IDS, but takes longer for intubation, when compared to the Macintosh laryngoscope in children.

Int J Paediatr Dent. 2019 Mar 19. doi: 10.1111/ipd.12497. [Epub ahead of print]

Effect of a relaxation training exercise on behaviour, anxiety, and pain during buccal infiltration anaesthesia in children: Randomized clinical trial.

Sridhar S, Suprabha BS, Shenoy R, Shwetha KT, Rao A.
India

BACKGROUND:
Cognitive behavioural techniques can decrease procedural pain and anxiety in children. Bubble breath exercise, a play therapy technique, may be used as a relaxation strategy to manage anxiety and pain. The objective of the study was to evaluate the effect of bubble breath exercise on dental anxiety, dental behaviour, and pain intensity during buccal infiltration of local anaesthetic in children.

STUDY DESIGN:
This randomized controlled trial involved 66 children aged 7-11 years, randomly allocated to two groups: Group 1 (control) and Group 2 (intervention group). Group 2 was trained in bubble breath exercise. The reaction during buccal infiltration anaesthesia was recorded in terms of behaviour (Frankl's behaviour rating scale), anxiety (Facial Image Scale and pulse rate), and pain perception (Wong-Baker FACES pain rating scale and the Faces, Leg, Activity, Cry, and Consolability scale).

RESULTS:
The bubble breath exercise significantly reduced the pain perceived, as measured by both the **Wong-Baker FACES pain rating scale** ($P < 0.001$) and the FLACC scale ($P < 0.001$). There was no statistically significant difference in dental anxiety and behaviour among the groups.

CONCLUSION:
Use of bubble breath exercise may be beneficial in decreasing the pain perceived during maxillary buccal infiltration anaesthesia in 7- to 11-year-old children.

Intensive care

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

Colomb Med (Cali). 2018 Jun 30;49(2):148-153. doi: 10.25100/cm.v49i2.2273. (Open access available)

As-needed endotracheal suctioning protocol vs a routine endotracheal suctioning in Pediatric Intensive Care Unit: A randomized controlled trial.

Lema-Zuluaga GL, Fernandez-Laverde M, Correa-Varela AM, Zuleta-Tobón JJ.
Colombia

Objective:
To compare two endotracheal suctioning protocols according to morbidity, days of mechanical ventilation, length of stay in the Pediatric Intensive Care Unit (PICU), incidence of Ventilator-Associated Pneumonia (VAP) and mortality.

Methods:
A Pragmatic randomized controlled trial performed at University Hospital Pablo Tobón Uribe, Medellin-Colombia. Forty-five children underwent an as-needed endotracheal suctioning protocol and forty five underwent a routine endotracheal suctioning protocol. Composite primary end point was the presence of hypoxemia, arrhythmias, accidental extubation and heart arrest. A logistic function trough generalized estimating equations (GEE) were used to calculate the Relative Risk for the main outcome.

Results:

Characteristics of patients were similar between groups. The composite primary end point was found in 22 (47%) of intervention group and 25 (55%) children of control group (RR= 0.84; 95% CI: 0.56-1.25), as well in 35 (5.8%) of 606 endotracheal suctioning performed to intervention group and 48 (7.4%) of 649 performed to control group (OR= 0.80; 95% CI: 0.5-1.3).

Conclusions:
There were no differences between an as-needed and a routine endotracheal suctioning protocol.

Childs Nerv Syst. 2019 Mar 16. doi: 10.1007/s00381-019-04121-3. [Epub ahead of print]

Comparison of equiosmolar dose of hyperosmolar agents in reducing intracranial pressure-a randomized control study in pediatric traumatic brain injury.

Kumar SA, Devi BI, Reddy M, Shukla D.
India

INTRODUCTION:
There are no comparative studies available for hyperosmolar therapy in children. The present study is a prospective open label randomized control trial to compare the effect of equiosmolar doses of mannitol and hypertonic saline in reducing intracranial pressure in children who sustained severe traumatic brain injury.

METHODS:
This is a prospective open-label randomized controlled trial. Thirty children aged less than or equal to 16 years with severe traumatic brain injury and raised intracranial pressure as measured by ventricular catheter insertion were enrolled. **Sixteen children received 20% mannitol, and 14 children received 3% saline as 2.5 ml/kg bolus for episodes of intracranial pressure above cutoff value for age.** The mean reduction in intracranial pressure and Glasgow outcome scale at 6 months after injury was measured.

RESULTS:
The mean reduction in intracranial pressure in mannitol group was 7.13 mmHg and in hypertonic saline group was 5.67 mmHg, and the difference was not statistically significant, p = 0.33. The incidence of death or survival in vegetative state was 23.07% in mannitol group and 16.66% in hypertonic saline group, and the difference was not statistically significant, p = 0.69.

CONCLUSION:
Both mannitol and hypertonic saline were equally effective for treatment of raised intracranial pressure in children with severe traumatic brain injury.

Comment
Under-powered study.

Antibiotics

Azithromycin mass drug administration

(see also Ophthalmology - Trachoma)

*** Am J Trop Med Hyg. 2019 Mar;100(3):691-695. doi: 10.4269/ajtmh.18-0846. (Open access available)

Mass Azithromycin Distribution to Prevent Childhood Mortality: A Pooled Analysis of Cluster-Randomized Trials.

Oldenburg CE, Arzika AM, Amza A, Gebre T, Kalua K, Mrango Z, Cotter SY, West SK, Bailey RL, Emerson PM, O'Brien KS, Porco TC, Keenan JD, Lietman TM.
USA, Niger, Ethiopia, Tanzania, UK

Abstract
Mass drug administration (MDA) with azithromycin may reduce under-5 child mortality (U5M) in sub-Saharan Africa. Here, we conducted **a pooled analysis of all published cluster-randomized trials evaluating the effect of azithromycin MDA on child mortality**. We pooled data from cluster-randomized trials randomizing communities to azithromycin MDA versus control. We calculated mortality rates in the azithromycin and control arms in each study, and by country for multisite studies including multiple countries. We conducted a two-stage individual community data meta-analysis to estimate the effect of azithromycin for prevention of child mortality. Three randomized controlled trials in four countries (Ethiopia, Malawi, Niger, and Tanzania) were identified. The overall pooled mortality rate was 15.9 per 1,000 person-years (95% confidence interval [CI]: 15.5-16.3). **The pooled mortality rate was lower in azithromycin-treated communities than in placebo-treated communities (14.7 deaths per 1,000 person-years, 95% CI: 14.2-15.3 versus 17.2 deaths per 1,000 person-years, 95% CI: 16.5-17.8). There was a 14.4% reduction in all-cause child mortality in communities receiving azithromycin MDA (95% CI: 6.3-21.7% reduction, *P* = 0.0007).** All-cause U5M was lower in communities receiving azithromycin MDA than in control communities, suggesting that azithromycin MDA could be a new tool to reduce child mortality in sub-Saharan Africa. However, heterogeneity in effect estimates suggests that the magnitude of the effect may vary in time and space and is currently not predictable.

Comment
The majority of the effect in these trials was in Niger.

N Engl J Med. 2019 Jun 6;380(23):2207-2214. doi: 10.1056/NEJMoa1817213.

Longer-Term Assessment of Azithromycin for Reducing Childhood Mortality in Africa.

Keenan JD, Arzika AM, Maliki R, Boubacar N, Elh Adamou S, Moussa Ali M, Cook C, Lebas E, Lin Y, Ray KJ, O'Brien KS, Doan T, Oldenburg CE, Callahan EK, Emerson PM, Porco TC, Lietman TM
All authors affilliations in USA

BACKGROUND:
The MORDOR I trial (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) showed that in Niger, mass administration of azithromycin twice a year for 2 years resulted in 18% lower postneonatal childhood mortality than administration of placebo. Whether this benefit could increase with each administration or wane owing to antibiotic resistance was unknown.
METHODS:
In the Niger component of the MORDOR I trial, we randomly assigned 594 communities to four twice-yearly distributions of either azithromycin or placebo to children 1 to 59 months of age. In MORDOR II, all these communities received two additional open-label azithromycin distributions. All-cause mortality was assessed twice yearly by census workers who were unaware of participants' original assignments.
RESULTS:
In the MORDOR II trial, the mean (±SD) azithromycin coverage was 91.3±7.2% in the communities that received twice-yearly azithromycin for the first time (i.e., had received placebo for 2 years in MORDOR I) and 92.0±6.6% in communities that received azithromycin for the third year (i.e., had received azithromycin for 2 years in MORDOR I). In MORDOR II, mortality was 24.0 per 1000 person-years (95% confidence interval [CI], 22.1 to 26.3) in communities that had originally received placebo in the first year and 23.3 per 1000 person-years (95% CI, 21.4 to 25.5) in those that had originally received azithromycin in the first year, with no significant difference between groups (P = 0.55). In communities that had originally received placebo, mortality decreased by 13.3% (95% CI, 5.8 to 20.2) when the communities received azithromycin (P = 0.007). In communities that had originally received azithromycin and continued receiving it for an additional year, the difference in mortality between the third year and the first 2 years was not significant (-3.6%; 95% CI, -12.3 to 4.5; P = 0.50).
CONCLUSIONS:
We found no evidence that the effect of mass administration of azithromycin on childhood mortality in Niger waned in the third year of treatment. Childhood mortality decreased when communities that had originally received placebo received azithromycin.

PLoS Negl Trop Dis. 2018 Nov 12;12(11):e0006950. doi: 10.1371/journal.pntd.0006950. eCollection 2018 Nov. (Open access available)

Safety of azithromycin in infants under six months of age in Niger: A community randomized trial.

Oldenburg CE, Arzika AM, Maliki R, Kane MS, Lebas E, Ray KJ, Cook C, Cotter SY, Zhou Z, West SK, Bailey R, Porco TC, Keenan JD, Lietman TM; MORDOR Study Group.
USA, Niger, UK

Abstract
BACKGROUND:
Mass azithromycin distribution reduces under-5 child mortality. Trachoma control programs currently treat infants aged 6 months and older. Here, we report findings from an infant

adverse event survey in 1-5 month olds who received azithromycin as part of a large community-randomized trial in Niger.

METHODS AND PRINCIPAL FINDINGS:
Active surveillance of infants aged 1-5 months at the time of treatment was conducted in 30 randomly selected communities from within a large cluster randomized trial of biannual mass azithromycin distribution compared to placebo to assess the potential impact on child mortality. **We compared the distribution of adverse events reported after treatment among azithromycin-treated versus placebo-treated infants.** From January 2015 to February 2018, the caregivers of 1,712 infants were surveyed. **Approximately one-third of caregivers reported at least one adverse event (azithromycin: 29.6%, placebo: 34.3%, risk ratio [RR] 0.86, 95% confidence interval [CI] 0.68 to 1.10, P = 0.23**). The most commonly reported adverse events included diarrhea (azithromycin: 19.3%, placebo: 28.1%, RR 0.68, 95% CI 0.49 to 0.96, P = 0.03), vomiting (azithromycin: 15.9%, placebo: 21.0%, RR 0.76, 95% CI 0.56 to 1.02, P = 0.07), and skin rash (azithromycin: 12.3%, placebo: 13.6%, RR 0.90, 95% CI 0.59 to 1.37, P = 0.63). No cases of infantile hypertrophic pyloric stenosis were reported.

CONCLUSIONS:
Azithromycin given to infants aged 1-5 months appeared to be safe. Inclusion of younger infants in larger azithromycin-based child mortality or trachoma control programs could be considered if deemed effective.

Open Forum Infect Dis. 2019 Feb 6;6(3):ofz061. doi: 10.1093/ofid/ofz061. eCollection 2019 Mar. (Open access available)

Indirect Effect of Azithromycin Use on the Intestinal Microbiome Diversity of Untreated Children: A Randomized Trial.

Oldenburg CE, Sié A, Coulibaly B, Ouermi L, Dah C, Tapsoba C, Bärnighausen T, Lebas E, Arzika AM, Cummings S, Zhong L, Lietman TM, Keenan JD, Doan T.
USA, Niger, Tanzania, UK

Abstract
Cohabiting children may share components of their intestinal microbiome. We evaluated whether receipt of azithromycin in one sibling confers changes to the intestinal microbiome in an untreated sibling compared with placebo in a randomized controlled trial. We found no evidence of an indirect effect of antibiotic use in cohabiting children.

Am J Trop Med Hyg. 2018 Sep;99(3):789-796. doi: 10.4269/ajtmh.18-0342. Epub 2018 Jul 12. (Open access available)

Effect of Antibiotics on Short-Term Growth among Children in Burkina Faso: A Randomized Trial.

Sié A , Dah C, Ouermi L, Tapsoba C, Zabre P, Bärnighausen T, Lebas E, Arzika AM, Snyder BM, Porco TC, Lietman TM, Keenan JD, Oldenburg CE.
Burkina Faso, USA, Niger

Abstract
Antibiotics improve both weight and height gain in randomized trials of preschool children with preexisting morbidity. Here, we assess the effect of a short course of three different antibiotics (amoxicillin, azithromycin, and cotrimoxazole) on short-term linear and ponderal growth in a population-based sample of preschool children in rural Burkina Faso. **We randomized households with at least two children in the Nouna district, Burkina Faso, to a 5-day course of amoxicillin, azithromycin, cotrimoxazole, or placebo.** Within each antibiotic-randomized household, one child was randomly assigned to receive the antibiotic and the other to receive the placebo. Weight and height measurements were taken at baseline and 30 days following the last study medication dose. Weight-for-height *Z* (WHZ), height-for-age *Z* (HAZ), and weight-for-age *Z* (WAZ) scoreswere calculated based on the 2006 World Health Organization standards. Of the 124 households and 248 children enrolled, 229 had anthropometry measurements at 1 month and were analyzed. **Children randomized to amoxicillin gained significantly more weight compared with both the placebo household (mean difference 317 g, 95% confidence interval [CI]: 115-519 g) and placebo sibling (mean difference 315 g, 95% CI: 147-482 g) controls**. Growth velocity in g/kg/day, and WHZ and WAZ scores were higher in amoxicillin-treated children compared with placebo households and siblings. There were no differences in weight gain in children randomized to azithromycin or cotrimoxazole compared with placebo households or placebo siblings. There were no differences in height gain or HAZ across any of the study arms. Amoxicillin may have short-term growth-promoting effects in healthy children.

PLoS Negl Trop Dis. 2019 Jun 5;13(6):e0007442. doi: 10.1371/journal.pntd.0007442. eCollection 2019 Jun. (Open Access available)

Linear growth in preschool children treated with mass azithromycin distributions for trachoma: A cluster-randomized trial.

Keenan JD, Gebresillasie S, Stoller NE, Haile BA, Tadesse Z, Cotter SY, Ray KJ, Aiemjoy K, Porco TC, Callahan EK, Emerson PM, Lietman TM
United States of America, Ethiopia

BACKGROUND:
Mass azithromycin distributions have been shown to reduce mortality among pre-school children in sub-Saharan Africa. It is unclear what mediates this mortality reduction, but one possibility is that antibiotics function as growth promoters for young children.
METHODS AND FINDINGS:
24 rural Ethiopian communities that had received biannual mass azithromycin distributions over the previous four years were enrolled in a parallel-group, cluster-randomized trial. Communities were randomized in a 1:1 ratio to either continuation of biannual oral azithromycin (20mg/kg for children, 1 g for adults) or to no programmatic antibiotics over the 36 months of the study period. All community members 6 months and older were eligible

for the intervention. The primary outcome was ocular chlamydia; height and weight were measured as secondary outcomes on children less than 60 months of age at months 12 and 36. Study participants were not masked; anthropometrists were not informed of the treatment allocation. Anthropometric measurements were collected for 282 children aged 0-36 months at the month 12 assessment and 455 children aged 0-59 months at the month 36 assessment, including 207 children who had measurements at both time points. After adjusting for age and sex, children were slightly but not significantly taller in the biannually treated communities (84.0 cm, 95%CI 83.2-84.8, in the azithromycin-treated communities vs. 83.7 cm, 95%CI 82.9-84.5, in the untreated communities; mean difference 0.31 cm, 95%CI -0.85 to 1.47, P = 0.60). No adverse events were reported.
CONCLUSIONS:
Periodic mass azithromycin distributions for trachoma did not demonstrate a strong impact on childhood growth.

Antibiotic resistance and stewardship

Daru. 2019 Feb 21. doi: 10.1007/s40199-019-00248-5. [Epub ahead of print] (Open access available)

Effectiveness of audit and feedback in addressing over prescribing of antibiotics and injectable medicines in a middle-income country: an RCT.

Soleymani F, Rashidian A, Hosseini M, Dinarvand R, Kebriaeezade A, Abdollahi M.
Iran

Overprescribing of antibiotics and injectable medicines is common in ambulatory care in many low- and middleincome countries. We evaluated the effects of three different interventions in improving physician prescribing. We conducted **a four-armed randomized controlled trial with one-month and three- months follow-up**. General physicians, pediatricians, and infectious disease specialists were included in this study if they had an outpatient office in Tehran, Iran. The study involved two behaviorally guided interventions: "new-design audit and feedback (NA&F)"; "printed educational material (PEM)" and an existing intervention of "routinely conducted audit and feedback (RA&F)". The theoretical framework underpinning the intervention was the theory of planned behavior. Main outcome measures were the percentage change in the proportion of prescriptions containing injectable dexamethasone; oral amoxicillin and cefixime. **NA&F reduced the proportion of prescriptions particularly those containing dexamethasone injectable and cefixime** (1.64, 0.99 absolute percentage change, p = 0.006, p = 0.01 respectively). PEM reduced the proportion of prescriptions containing cefixime (0.93 absolute percentage change p = 0.04). Other primary outcomes had no significant differences. A secondary outcome measure showed overall prescribing of injectables also reduced (absolute risk reduction: 3%). Overally, the study provides strong evidence that using theoretical insights in the development of the intervention improved prescribing behavior that lasted at least three months after the intervention. The design, format, and presentation of messages in feedback forms significantly influence the impact of audit and feedback on physician prescribing.

While the interventions were effective, the impacts on inappropriate prescribing were modest and limited. In settings with rampant problems of overprescribing, intensive interventions are required to substantially improve prescribing patterns.

PLoS Med. 2019 Feb 5;16(2):e1002733. doi: 10.1371/journal.pmed.1002733. eCollection 2019 Feb. (Open access available)

Long-term outcomes of an educational intervention to reduce antibiotic prescribing for childhood upper respiratory tract infections in rural China: Follow-up of a cluster-randomised controlled trial.

Wei X, Zhang Z, Hicks JP, Walley JD, King R, Newell JN, Yin J, Zeng J, Guo Y, Lin M, Upshur REG, Sun Q.
Canada, China, UK

BACKGROUND:
Inappropriate antibiotic prescribing causes widespread serious health problems. To reduce prescribing of antibiotics in Chinese primary care to children with upper respiratory tract infections (URTIs), we developed an **intervention comprising clinical guidelines, monthly prescribing review meetings, doctor-patient communication skills training, and education materials for caregivers. We previously evaluated our intervention using an unblinded cluster-randomised controlled trial (cRCT) in 25 primary care facilities across two rural counties.** When our trial ended at the 6-month follow-up period, we found that the intervention had reduced antibiotic prescribing for childhood URTIs by 29 percentage points (pp) (95% CI -42 to -16).

METHODS AND FINDINGS:
In this long-term follow-up study, we collected our trial outcomes from the one county (14 facilities and 1:1 cluster randomisation ratio) that had electronic records available 12 months after the trial ended, at the 18-month follow-up period. **Our primary outcome was the antibiotic prescription rate (APR)-the percentage of outpatient prescriptions containing any antibiotic(s) for children aged 2 to 14 years who had a primary diagnosis of a URTI and had no other illness requiring antibiotics.** We also conducted 15 in-depth interviews to understand how interventions were sustained. In intervention facilities, the APR was 84% (1,171 out of 1,400) at baseline, 37% (515 out of 1,380) at 6 months, and 54% (2,748 out of 5,084) at 18 months, and in control facilities, it was 76% (1,063 out of 1,400), 77% (1,084 out of 1,400), and 75% (2,772 out of 3,685), respectively. **After adjusting for patient and prescribing doctor covariates, compared to the baseline intervention-control difference, the difference at 6 months represented a 6-month intervention-arm reduction in the APR of -49 pp (95% CI -63 to -35; P < 0.0001), and compared to the baseline difference, the difference at 18 months represented an 18-month intervention-arm reduction in the APR of -36 pp (95% CI -55 to -17; P < 0.0001).** Compared to the 6-month intervention-control difference, the difference at 18 months represented no change in the APR: 13 pp (95% CI -7 to 33; P = 0.21). Factors reported to sustain reductions in antibiotic prescribing included doctors' improved knowledge and communication skills and focused prescription review meetings, whereas lack of supervision and monitoring may be associated

with relapse. Key limitations were not including all clusters from the trial and not collecting returned visits or sepsis cases.

CONCLUSIONS:
Our intervention was associated with sustained and substantial reductions in antibiotic prescribing at the end of the intervention period and 12 months later. Our intervention may be adapted to similar resource-poor settings.

Lancet Glob Health. 2019 Jan;7(1):e119-e131. doi: 10.1016/S2214-109X(18)30444-3. (Open access available)

Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial.

Althaus T, Greer RC, Swe MMM, Cohen J, Tun NN, Heaton J, Nedsuwan S, Intralawan D, Sumpradit N, Dittrich S, Doran Z, Waithira N, Thu HM, Win H, Thaipadungpanit J, Srilohasin P, Mukaka M, Smit PW, Charoenboon EN, Haenssgen MJ, Wangrangsimakul T, Blacksell S, Limmathurotsakul D, Day N, Smithuis F, Lubell Y.
Thailand, Myanmar, UK

BACKGROUND:
In southeast Asia, antibiotic prescription in febrile patients attending primary care is common, and a probable contributor to the high burden of antimicrobial resistance. The objective of this trial was to explore whether C-reactive protein (CRP) testing at point of care could rationalise antibiotic prescription in primary care, comparing two proposed thresholds to classify CRP concentrations as low or high to guide antibiotic treatment.

METHODS:
We did a multicentre, open-label, randomised, controlled trial in participants aged at least 1 year with a documented fever or a chief complaint of fever (regardless of previous antibiotic intake and comorbidities other than malignancies) recruited from six public primary care units in Thailand and three primary care clinics and one outpatient department in Myanmar**. Individuals were randomly assigned using a computer-based randomisation system at a ratio of 1:1:1 to either the control group or one of two CRP testing groups, which used thresholds of 20 mg/L (group A) or 40 mg/L CRP (group B) to guide antibiotic prescription.** Health-care providers were masked to allocation between the two intervention groups but not to the control group. **The primary outcome was the prescription of any antibiotic from day 0 to day 5 and the proportion of patients who were prescribed an antibiotic when CRP concentrations were above and below the 20 mg/L or 40 mg/L thresholds.** The primary outcome was analysed in the intention-to-treat and per-protocol populations. The trial is registered with ClinicalTrials.gov, number NCT02758821, and is now completed.

FINDINGS:

Between June 8, 2016, and Aug 25, 2017, we recruited 2410 patients, of whom 803 patients were randomly assigned to CRP group A, 800 to CRP group B, and 807 to the control group. 598 patients in CRP group A, 593 in CRP group B, and 767 in the control group had follow-up data for both day 5 and day 14 and had been prescribed antibiotics (or not) in accordance with test results (per-protocol population). **During the trial, 318 (39%) of 807 patients in the control group were prescribed an antibiotic by day 5, compared with 290 (36%) of 803 patients in CRP group A and 275 (34%) of 800 in CRP group B.** The adjusted odds ratio (aOR) of 0·80 (95% CI 0·65-0·98) and risk difference of -5·0 percentage points (95% CI -9·7 to -0·3) between group B and the control group were significant, although lower than anticipated, whereas the reduction in prescribing in group A compared with the control group was not significant (aOR 0·86 [0·70-1·06]; risk difference -3·3 percentage points [-8·0 to 1·4]). Patients with high CRP concentrations in both intervention groups were more likely to be prescribed an antibiotic than in the control group (CRP ≥20 mg/L: group A vs control group, p<0·0001; CRP ≥40 mg/L: group B vs control group, p<0·0001), and those with low CRP concentrations were more likely to have an antibiotic withheld (CRP <20 mg/L: group A vs control group, p<0·0001; CRP <40 mg/L: group B vs control group, p<0·0001). 24 serious adverse events were recorded, consisting of 23 hospital admissions and one death, which occurred in CRP group A. Only one serious adverse event was thought to be possibly related to the study (a hospital admission in CRP group A).

INTERPRETATION:
In febrile patients attending primary care, testing for CRP at point of care with a threshold of 40 mg/L resulted in a modest but significant reduction in antibiotic prescribing, with patients with high CRP being more likely to be prescribed an antibiotic, and no evidence of a difference in clinical outcomes. This study extends the evidence base from lower-income settings supporting the use of CRP tests to rationalise antibiotic use in primary care patients with an acute febrile illness. A key limitation of this study is the individual rather than cluster randomised study design which might have resulted in contamination between the study groups, reducing the effect size of the intervention.

Clin Infect Dis. 2019 May 31. pii: ciz455. doi: 10.1093/cid/ciz455. [Epub ahead of print]

Gut resistome after oral antibiotics in preschool children in Burkina Faso: A randomized controlled trial.

Oldenburg CE, Hinterwirth A, Sié A, Coulibaly B, Ouermi L, Dah C, Tapsoba C, Cummings SL, Zhong L, Chen C, Sarkar S, Bärnighausen T, Lietman TM, Keenan JD, Doan T
USA, Burkina Faso, Germany, South Africa

Abstract
We evaluated the effect of systemic antibiotics (azithromycin, amoxicillin, cotrimoxazole, or placebo) on the gut resistome in children aged 6-59 months in a randomized controlled trial. Azithromycin and cotrimoxazole led to an increase in macrolide and sulfonamide resistance determinants. Resistome expansion can be induced with a single course of antibiotics.

Community health workers and education

BMC Med Educ. 2018 Sep 27;18(1):224. doi: 10.1186/s12909-018-1332-x. (Open access available)

Effectiveness of an action-oriented educational intervention in ensuring long term improvement of knowledge, attitudes and practices of community health workers in maternal and infant health: a randomized controlled study.

Melo E Lima TR, Maia PFCMD, Valente EP, Vezzini F, Tamburlini G.
Brazil, Italy

BACKGROUND:
The potential role of Community Health Workers (CHWs) in improving maternal and child health outcomes, particularly in low and middle-income countries and in disadvantaged communities, is receiving increased attention. Adequate and focused training is among the key requisites for enhancing CHWs performances and research is necessary to identify effective training methods.

METHODS:
A randomized controlled study was designed to assess the effectiveness of a training course in improving knowledge, attitudes and practices (KAP) of CHWs regarding maternal and infant health. **Seventy-eight CHWs** belonging to Family Health Units in the city of Recife, Brazil were randomly allocated to intervention and control groups. **The intervention group took part in a four-day interactive training course based on an action-oriented guide to perform home visits to pregnant women and their infants throughout pregnancy and infancy until 9 months of age.** KAP in intervention group after training and after 1 year were compared to control group and to baseline.

RESULTS:
Fifty-nine CHWs completed all KAP assessments (31 in intervention and 28 in control group). Baseline characteristics were similar in both groups. **At 1 year from training, the intervention group had higher overall KAP score (120.65 vs. 108.19, p < 0.001) as well as knowledge (47.45 vs. 40.54, p < 0.001), practice (53.45 vs. 49.11, p < 0.001) and attitudes scores (19.74 vs. 18.81, p = 0.047) than the control group.** Moreover, at 1 year from training, the intervention group maintained significant improvements in overall KAP score (120.65 vs. 106.55, p < 0.001) as well as in knowledge (45.45 vs. 42.13, p < 0.001), and practice (53.45 vs. 45.29, p < 0.001) scores with respect to baseline. In the control group, overall KAP (106.59 vs. 108.19, p = 0.345) as well as separate knowledge, attitudes and practices scores remained unchanged.

CONCLUSIONS:

A four-day interactive training course on action-oriented home visits to pregnant women and infants produced a sustained improvement of CHWs' KAP and may represent a model to ensure retention of acquired competences.

Cash transfers and family economic support

Soc Sci Med. 2019 May;228:17-24. doi: 10.1016/j.socscimed.2019.03.003. Epub 2019 Mar 7. (Open access available)

Poverty, economic strengthening, and mental health among AIDS orphaned children in Uganda: Mediation model in a randomized clinical trial.

Karimli L, Ssewamala FM, Neilands TB, Wells CR, Bermudez LG.

Uganda

Some evidence points to the positive effects of asset accumulation programs on mental health of children living in low-resource contexts. However, no evidence exists as to why and how such impact occurs. Our study aims to understand whether child poverty, child work, and household wealth serve as pathways through which the economic strengthening intervention affects the mental health of AIDS-orphaned children. **The study employed a cluster-randomized experimental design with a family-based economic strengthening intervention conducted among 1410 school-going AIDS-orphaned children ages 10 and 16 years old in 48 primary schools in South Western Uganda**. To test the hypothesized relationships between the intervention, mediators (household wealth, child poverty, and child's work) and mental health, we ran structural equation models that adjust for clustering of individuals within schools and account for potential correlation among the mediators. **We found significant unmediated effect of the intervention on children's mental health at 24 months (B = -0.59; 95% CI: 0.93, -0.25; p < 0.001; β = -0.33). Furthermore, the results suggest that participation in the intervention reduced child poverty at 12 months, which in turn improved latent mental health outcome at 24 months (B = -0.14; 95% CI: -0.29, -0.01; p < 0.06; β = -0.08).** In addition, though not statistically significant at the 0.05 level, at 36 and 48 months, mental health of children in the treatment group improved by 0.13 and 0.16 standard deviation points correspondingly with no evidence of mediation. **Our findings suggest that anti-poverty programs that aim solely to improve household income may be less advantageous to children's mental health as compared to those that are specifically targeted towards reducing the impact of poverty on children.** Further studies using more comprehensive measures of child work and age-appropriate child mental health may shed more light on understanding the link between asset accumulation interventions, child labor and children's mental health.

Community health and health education

Hum Resour Health. 2019 Mar 29;17(1):23. doi: 10.1186/s12960-019-0355-7. (Open access available)

The effect of a community health worker intervention on public satisfaction: evidence from an unregistered outcome in a cluster-randomized controlled trial in Dar es Salaam, Tanzania.

Larson E, Geldsetzer P, Mboggo E, Lema IA, Sando D, Ekström AM, Fawzi W, Foster DW, Kilewo C, Li N, Machumi L, Magesa L, Mujinja P, Mungure E, Mwanyika-Sando M, Naburi H, Siril H, Spiegelman D, Ulenga N, Bärnighausen T.
Tanzania

BACKGROUND:
There is a dearth of evidence on the causal effects of different care delivery approaches on health system satisfaction. A better understanding of public satisfaction with the health system is particularly important within the context of task shifting to community health workers (CHWs). This paper determines the effects of a CHW program focused on maternal health services on public satisfaction with the health system among women who are pregnant or have recently delivered.

METHODS:
From January 2013 to April 2014, we carried out a cluster-randomized controlled health system implementation trial of a CHW program. **Sixty wards in Dar es Salaam, Tanzania, were randomly allocated to either a maternal health CHW program (36 wards) or the standard of care (24 wards).** From May to August 2014, we interviewed a random sample of women who were either currently pregnant or had recently delivered a child. We used five-level Likert scales to assess women's satisfaction with the CHW program and with the public-sector health system in Dar es Salaam.

RESULTS:
In total, 2329 women participated in the survey (response rate 90.2%). Households in intervention areas were 2.3 times as likely as households in control areas to have ever received a CHW visit (95% CI 1.8, 3.0). The intervention led to a 16-percentage-point increase in women reporting they were satisfied or very satisfied with the CHW program (95% CI 3, 30) and a 15-percentage-point increase in satisfaction with the public-sector health system (95% CI 3, 27).

CONCLUSIONS:
A CHW program for maternal and child health in Tanzania achieved better public satisfaction than the standard CHW program. Policy-makers and implementers who are involved in designing and organizing CHW programs should consider the potential positive impact of the program on public satisfaction.

J Glob Health. 2019 Jun;9(1):010418. doi: 10.7189/jogh.09.010418. (Open access available)

Piloting a participatory, community-based health information system for strengthening community-based health services: findings of a cluster-randomized controlled trial in the slums of Freetown, Sierra Leone.

O'Connor EC, Hutain J, Christensen M, Kamara MS, Conteh A, Sarriot E, Samba TT, Perry HB.
Sierra Leonne

BACKGROUND:
Although community engagement has been promoted as a strategy for health systems strengthening, there is need for more evidence for effectiveness of this approach. We describe an operations research (OR) Study and assessment of one form of community engagement, the development and implementation of a **participatory community-based health information system (PCBHIS)**, in slum communities in Freetown, Sierra Leone.

METHODS:
A child survival project was implemented in 10 slum communities, which were then randomly allocated to intervention (PCBHIS) and comparison areas. In the 5 PCBHIS communities, the findings from monthly reports submitted by community health workers (CHWs) and verbal autopsy findings for deaths of children who died before reaching 5 years of age, were processed and shared at bimonthly meetings in each community. These meetings, called Community Health Data Review (CHDR) meetings, were attended by community leaders, including members of the Ward Development Committee (WDC) and Health Management Committee (HMC), by the CHW Peer Supervisors, and by representatives of the Peripheral Health Unit. Following a review of the information, attendees proposed actions to strengthen community-based health services in their community. These meetings were held over a period of 20 months from July 2015 to March 2017. At baseline and endline, knowledge, practice and coverage (KPC) surveys measured household health-related behaviors and care-seeking behaviors. The capacity of HMCs and WDCs to engage with the local health system was also measured at baseline and endline. Reports of CHW household contact and assessments of CHW quality were obtained in the endline KPC household survey, and household contacts measured in monthly submitted reports were also tabulated.

RESULTS:
The self-assessment scores of WDCs' capacity to fulfil their roles improved more in the intervention than in the comparison area for all six components, but for only 1 of the 6 was the improvement statistically significant (monthly and quarterly meetings in which Peer Supervisor and/or CHW supervision was an agenda item). The scores for the HMCs improved *less* in the intervention area than in the comparison area for all six components, but none of these differences were statistically significant. Topics of discussion in CHDRs focused primarily on CHW functionality. **All three indicators of CHW functioning (as measured by reports submitted from CHWs) improved more in the intervention area relative to the comparison area**, with 2 out of 3 measures of improvement reaching statistical significance. **Five of 7 household behaviors judged to be amenable to promotion by CHWs improved more in the intervention area than in the comparison area, and 2 out of the 5 were statistically significant (feeding colostrum and appropriate infant and young child feeding). Four of the 6 care-seeking behaviors**

judged to be amenable to promotion by CHWs improved more in the intervention area than in the comparison area, and 1 was statistically significant (treatment of diarrhea with ORS and zinc). None of the findings that favored the comparison area were statistically significant.

CONCLUSIONS:
This study was implemented in challenging circumstances. The OR Study intervention was delayed because of interruptions in finalizing the national CHW policy, two separate cholera epidemics, and the Ebola epidemic lasting more than 2 years. Weaknesses in the CHW intervention severely limited the extent to which the PCBHIS could be used to observe trends in mortality and morbidity. **Nonetheless, the positive results achieved in the area of functionality of the CHW intervention and community structure capacity are encouraging**. Results suggest there is value in further methodologically rigorous investigations into improving community-based health system functioning through a similar approach to community engagement.

PLoS One. 2019 Feb 28;14(2):e0212847. doi: 10.1371/journal.pone.0212847. eCollection 2019. (Open access available)

Strengthening the community support group to improve maternal and neonatal health seeking behaviors: A cluster-randomized controlled trial in Satkhira District, Bangladesh.

Gai Tobe R, Islam MT, Yoshimura Y, Hossain J.
Bangladesh

BACKGROUND:
Although achieved development goals on maternal and child health, in the era of Sustainable Development Goals (SDGs), Bangladesh still needs to promote skilled attendance at birth as well as a continuum of care for mothers and babies. How to implement effective interventions by strengthening the community health system also remains as a crucial policy issue. The objective of the proposed study is to evaluate the impact of a community-based intervention as part of a bilateral development aid project on utilization of maternal and neonatal care provided by skilled providers and qualified facilities.

METHODS:
A cluster randomized trial was conducted in Kalaroa Upazila of Satkhira District. Community Clinics (CCs) in the study setting were randomly allocated to either intervention or control. We recruited all eligible women covered by CC catchment areas who gave a birth during the past 12 months of data collection at the baseline and end-line surveys. In the intervention areas, three Community Support Groups (CSGs) were developed in each of the CC areas. The members of CSG were trained to identify pregnant women, educate community people on pregnancy related danger signs, and encourage them for utilization of skilled services in the community and health facilities. The primary outcomes were the utilization of services for antenatal care, delivery, postnatal care and sick newborns. Difference-in-Difference (DID)

analysis was performed to identify the changes by the intervention with adjustment of cluster effects by generalized mixed effects regression models.

RESULT:
The major indicators of the utilization of maternal and neonatal care among pregnant women with different wealth status showed significant improvement after the intervention. The impacts of the intervention were in particular significant among the women of 2nd and 3rd quintiles of household wealth status. The use of CCs increased after the intervention and private hospitals / clinics served as the major health providers. The study also identified increased practices of cesarean section.

CONCLUSION:
The success of the intervention suggests a potential of the government efforts to strengthen the community support system for promotion of safe motherhood. The intervention helps to identify and remove existing and emerging barriers that lie between women and healthcare providers for safe motherhood and continuum of care.

Child protection and family violence

PLoS One. 2019 Feb 7;14(2):e0211361. doi: 10.1371/journal.pone.0211361. eCollection 2019. (Open access available)

Violence against Afghan women by husbands, mothers-in-law and siblings-in-law/siblings: Risk markers and health consequences in an analysis of the baseline of a randomised controlled trial.

Jewkes R, Corboz J, Gibbs A.
South Africa, Afghanistan

BACKGROUND:
Violence by mothers-in-law, as well as husbands, is a recognised problem in many countries. It has been given little attention in research on violence and its importance as a health problem, and aggravator of husband violence, has not been well established. Our aim was to describe patterns and the frequency of mother-in-law and sibling-in-law/sibling physical violence in relation to physical violence from husbands, and to describe risk characteristics and associated health behaviours of women with different abuse exposures.

METHODS:
1,463 women aged 18-48 were recruited into a randomised controlled trial (RCT) to evaluate a women empowerment intervention in 6 villages of Kabul and Nangarhar provinces. The women were interviewed at baseline. The analysis uses bi-variable and multivariable logistic regression.

RESULTS:

932 of the women were currently married. Of these, 14% of women experienced mother-in-law physical violence and 23.2% of women experienced physical spousal violence in the previous 12 months. For 7.0% of women, these exposures were combined. Physical violence was associated with food insecurity and having to borrow for food, being in a polygamous marriage, living with their mother-in-law, as well as province of residence (higher in Nangarhar). Women who had earnings were relatively protected. Whilst most mothers-in-law were described in positive terms, those who used physical violence were much less likely to be described so and a quarter were described as very strict and controlling and 16.8% as cruel. Overall slightly more women described their husband in positive terms than their mother-in-law, but there was a very strong correlation between the way in which husbands were perceived and the violence of their mothers. **Women's mental health (depression, suicidal thoughts and PTSD symptoms score), self-rated general health, disability and beating of their children were all strongly associated with intimate partner violence (IPV) exposure.** The strength of the association was much greater for all of these problems if the IPV was combined with physical violence from a mother-in-law or sibling-in-law/sibling. Experienced alone, violence from the mother-in-law or a sibling-in-law/sibling was associated with an elevated risk of all of these problems except depression.

INTERPRETATION:
Mother-in-law and sibling-in-law/sibling physical violence is an appreciable problem among the women studied in Afghanistan, linked to poverty. It has a major impact on women's health, componding the heath impact of IPV. In this setting conceptualising women's risk and exposure to violence at home as only in terms of IPV is inadequate and the framing of domestic violence much more appropriately captures women's risks and exposures. We suggest that it may be fruitful for many women to target violence prevention at the domestic unit rather than just at women and their husbands.

Cryptococcal infection

Cochrane Database Syst Rev. 2018 Jul 25;7:CD005647. doi: 10.1002/14651858.CD005647.pub3. (Open access available)

Treatment for HIV-associated cryptococcal meningitis.

Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, Ford N.
USA

BACKGROUND:
Cryptococcal meningitis is a severe fungal infection that occurs primarily in the setting of advanced immunodeficiency and remains a major cause of HIV-related deaths worldwide. **The best induction therapy to reduce mortality from HIV-associated cryptococcal meningitis is unclear**, particularly in resource-limited settings where management of drug-related toxicities associated with more potent antifungal drugs is a challenge.

OBJECTIVES:

To evaluate the best induction therapy to reduce mortality from HIV-associated cryptococcal meningitis; to compare side effect profiles of different therapies.

SEARCH METHODS:
We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE (PubMed), Embase (Ovid), LILACS (BIREME), African Index Medicus, and Index Medicus for the South-East Asia Region (IMSEAR) from 1 January 1980 to 9 July 2018. We also searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, and the ISRCTN registry; and abstracts of select conferences published between 1 July 2014 and 9 July 2018.

SELECTION CRITERIA:
We included randomized controlled trials that compared antifungal induction therapies used for the first episode of HIV-associated cryptococcal meningitis. Comparisons could include different individual or combination therapies, or the same antifungal therapies with differing durations of induction (less than two weeks or two or more weeks, the latter being the current standard of care). We included data regardless of age, geographical region, or drug dosage. We specified no language restriction.

DATA COLLECTION AND ANALYSIS:
Two review authors independently screened titles and abstracts identified by the search strategy. We obtained the full texts of potentially eligible studies to assess eligibility and extracted data using standardized forms. The main outcomes included mortality at 2 weeks, 10 weeks, and 6 months; mean rate of cerebrospinal fluid fungal clearance in the first two weeks of treatment; and Division of AIDS (DAIDS) grade three or four laboratory events. Using random-effects models we determined pooled risk ratio (RR) and 95% confidence interval (CI) for dichotomous outcomes and mean differences (MD) and 95% CI for continuous outcomes. For the direct comparison of 10-week mortality, we assessed the certainty of the evidence using the GRADE approach. We performed a network meta-analysis using multivariate meta-regression. We modelled treatment differences (RR and 95% CI) and determined treatment rankings for two-week and 10-week mortality outcomes using surface under the cumulative ranking curve (SUCRA). We assessed transitivity by comparing distribution of effect modifiers between studies, local inconsistency through a node-splitting approach, and global inconsistency using design-by-treatment interaction modelling. For the network meta-analysis, we applied a modified GRADE approach for assessing the certainty of the evidence for 10-week mortality.

MAIN RESULTS:
We included 13 eligible studies that enrolled 2426 participants and compared 21 interventions. All but two studies were conducted in resource-limited settings, including 11 of 12 studies with 10-week mortality data.In the direct pairwise comparisons evaluating 10-week mortality, one study from four sub-Saharan African countries contributed data to several key comparisons. **At 10 weeks these data showed that those on the regimen of one-week amphotericin B deoxycholate (AmBd) and flucytosine (5FC) followed by fluconazole (FLU) on days 8 to 14 had lower mortality when compared to (i) two weeks of AmBd and 5FC (RR 0.62, 95% CI 0.42 to 0.93; 228 participants, 1 study), (ii) two weeks of AmBd and FLU (RR 0.58, 95% CI 0.39 to 0.86; 227 participants, 1 study), (iii) one week**

of AmBd with two weeks of FLU (RR 0.49, 95% CI 0.34 to 0.72; 224 participants, 1 study), and (iv) two weeks of 5FC and FLU (RR 0.68, 95% CI 0.47 to 0.99; 338 participants, 1 study). The evidence for each of these comparisons was of moderate certainty. For other outcomes, this shortened one-week AmBd and 5FC regimen had similar fungal clearance (MD 0.05 $\log_{10}$ CFU/mL/day, 95% CI -0.02 to 0.12; 186 participants, 1 study) as well as lower risk of grade three or four anaemia (RR 0.31, 95% CI 0.16 to 0.60; 228 participants, 1 study) compared to the two-week regimen of AmBd and 5FC.For 10-week mortality, the comparison of two weeks of 5FC and FLU with two weeks of AmBd and 5FC (RR 0.92, 95% CI 0.69 to 1.23; 340 participants, 1 study) or two weeks of AmBd and FLU (RR 0.85, 95% CI 0.64 to 1.13; 339 participants, 1 study) did not show a difference in mortality, with moderate-certainty evidence for both comparisons.**When two weeks of combination AmBd and 5FC was compared with AmBd alone, pooled data showed lower mortality at 10 weeks (RR 0.66, 95% CI 0.46 to 0.95; 231 participants, 2 studies, moderate-certainty evidence).**When two weeks of AmBd and FLU was compared to AmBd alone, there was no difference in 10-week mortality in pooled data (RR 0.94, 95% CI 0.55 to 1.62; 371 participants, 3 studies, low-certainty evidence).**One week of AmBd and 5FC followed by FLU on days 8 to 14 was the best induction therapy regimen after comparison with 11 other regimens for 10-week mortality in the network meta-analysis**, with an overall SUCRA ranking of 88%.
AUTHORS' CONCLUSIONS:
In resource-limited settings, one-week AmBd- and 5FC-based therapy is probably superior to other regimens for treatment of HIV-associated cryptococcal meningitis. An all-oral regimen of two weeks 5FC and FLU may be an alternative in settings where AmBd is unavailable or intravenous therapy cannot be safely administered. We found no mortality benefit of combination two weeks AmBd and FLU compared to AmBd alone. Given the absence of data from studies in children, and limited data from high-income countries, our findings provide limited guidance for treatment in these patients and settings.

Cochrane Database Syst Rev. 2018 Aug 29;8:CD004773. doi: 10.1002/14651858.CD004773.pub3. (Open access available)

Primary antifungal prophylaxis for cryptococcal disease in HIV-positive people.

Awotiwon AA, Johnson S, Rutherford GW, Meintjes G, Eshun-Wilson I.
South Africa

BACKGROUND:
Cryptococcal disease remains one of the main causes of death in HIV-positive people who have low cluster of differentiation 4 (CD4) cell counts. Currently, the World Health Organization (WHO) recommends screening HIV-positive people with low CD4 counts for cryptococcal antigenaemia (CrAg), and treating those who are CrAg-positive. This Cochrane Review examined the effects of an approach where those with low CD4 counts received regular prophylactic antifungals, such as fluconazole.

OBJECTIVES:

To assess the efficacy and safety of antifungal drugs for the primary prevention of cryptococcal disease in adults and children who are HIV-positive.

SEARCH METHODS:
We searched the CENTRAL, MEDLINE PubMed, Embase OVID, CINAHL EBSCOHost, WHO International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, conference proceedings for the International AIDS Society (IAS) and Conference on Retroviruses and Opportunistic Infections (CROI), and reference lists of relevant articles up to 31 August 2017.

SELECTION CRITERIA:
Randomized controlled trials of adults and children, who are HIV-positive with low CD4 counts, without a current or prior diagnosis of cryptococcal disease that compared any antifungal drug taken as primary prophylaxis to placebo or standard care.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed eligibility and risk of bias, and extracted and analysed data. The primary outcome was all-cause mortality. We summarized all outcomes using risk ratios (RR) with 95% confidence intervals (CI). Where appropriate, we pooled data in meta-analyses. We assessed the certainty of the evidence using the GRADE approach.

MAIN RESULTS:
Nine trials, enrolling 5426 participants, met the inclusion criteria of this review. Six trials administered fluconazole, while three trials administered itraconazole.Antifungal prophylaxis may make little or no difference to all-cause mortality (RR 1.07, 95% CI 0.80 to 1.43; 6 trials, 3220 participants; low-certainty evidence). For cryptococcal specific outcomes, **prophylaxis probably reduces the risk of developing cryptococcal disease (RR 0.29, 95% CI 0.17 to 0.49; 7 trials, 5000 participants; moderate-certainty evidence), and probably reduces deaths due to cryptococcal disease (RR 0.29, 95% CI 0.11 to 0.72; 5 trials, 3813 participants; moderate-certainty evidence).** Fluconazole prophylaxis may make no clear difference to the risk of developing clinically resistant Candida disease (RR 0.93, 95% CI 0.56 to 1.56; 3 trials, 1198 participants; low-certainty evidence); however, there may be an increased detection of fluconazole-resistant Candida isolates from surveillance cultures (RR 1.25, 95% CI 1.00 to 1.55; 3 trials, 539 participants; low-certainty evidence). Antifungal prophylaxis was generally well-tolerated with probably no clear difference in the risk of discontinuation of antifungal prophylaxis compared with placebo (RR 1.01, 95% CI 0.91 to 1.13; 4 trials, 2317 participants; moderate-certainty evidence). Antifungal prophylaxis may also make no difference to the risk of having any adverse event (RR 1.07, 95% CI 0.88 to 1.30; 4 trials, 2317 participants; low-certainty evidence), or a serious adverse event (RR 1.08, 95% CI 0.83 to 1.41; 4 trials, 888 participants; low-certainty evidence) when compared to placebo or standard care.

AUTHORS' CONCLUSIONS:
Antifungal prophylaxis reduced the risk of developing and dying from cryptococcal disease. Therefore, where CrAG screening is not available, antifungal prophylaxis may be used in patients with low CD4 counts at diagnosis and who are at risk of developing cryptococcal disease.

Dengue

(see Vaccines - dengue)

PLoS Negl Trop Dis. 2018 Oct 4;12(10):e0006497. doi: 10.1371/journal.pntd.0006497. eCollection 2018 Oct. (Open access available)
Development of standard clinical endpoints for use in dengue interventional trials.
Tomashek KM, Wills B, See Lum LC, Thomas L, Durbin A, Leo YS, de Bosch N, Rojas E, Hendrickx K, Erpicum M, Agulto L, Jaenisch T, Tissera H, Suntarattiwong P, Collers BA, Wallace D, Schmidt AC, Precioso A, Narvaez F, Thomas SJ, Edelman R, Siqueira JB, Cassetti MC, Dempsey W, Gubler DJ.
USA, Malaysia, France, Singapore, Venezuela, Colombia, Belgium, Thailand, Switzerland, Brazil, Nicaragua

Abstract
Dengue is a major public health problem worldwide. Although several drug candidates have been evaluated in randomized controlled trials, none has been effective and at present, early recognition of severe dengue and timely supportive care are used to reduce mortality. While the first dengue vaccine was recently licensed, and several other candidates are in late stage clinical trials, future decisions regarding widespread deployment of vaccines and/or therapeutics will require evidence of product safety, efficacy and effectiveness. Standard, quantifiable clinical endpoints are needed to ensure reproducibility and comparability of research findings. To address this need, we established a working group of dengue researchers and public health specialists to develop standardized endpoints and work towards consensus opinion on those endpoints. After discussion at two working group meetings and presentations at international conferences, a Delphi methodology-based query was used to finalize and operationalize the clinical endpoints. Participants were asked to select the best endpoints from proposed definitions or offer revised/new definitions, and to indicate whether contributing items should be designated as optional or required. After the third round of inquiry, 70% or greater agreement was reached on moderate and severe plasma leakage, moderate and severe bleeding, acute hepatitis and acute liver failure, and moderate and severe neurologic disease. There was less agreement regarding moderate and severe thrombocytopenia and moderate and severe myocarditis. Notably, 68% of participants agreed that a 50,000 to 20,000 mm3 platelet range be used to define moderate thrombocytopenia; however, they remained divided on whether a rapid decreasing trend or one platelet count should be case defining. While at least 70% agreement was reached on most endpoints, the process identified areas for further evaluation and standardization within the context of ongoing clinical studies. These endpoints can be used to harmonize data collection and improve comparability between dengue clinical trials.

Early childhood development

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

Curr Dev Nutr. 2019 Jun 13;3(Suppl 1). pii: nzz034.P10-003-19. doi: 10.1093/cdn/nzz034.P10-003-19. eCollection 2019 Jun.

Beyond Stunting: Mechanisms Linking Length to Early Child Development Among Infants in Rural India (P10-003-19).

Black M, Yimgang D, Hurley K, Harding K, Fernandez-Rao S, Balakrishna N, Radhakrishna K, Reinhart G, Nair K.
USA, India

Objectives:
In low and middle-income countries, early child development (ECD) is associated with stunting, but the association with length-for-age z-scores (LAZ) is understudied. The objective is to examine whether the association with ECD among infants extends beyond stunting to LAZ and whether it is altered by nurturance or inflammation.
Methods:
Sample: 513 infants (mean age 8.6 months, SD 2.2), 20% stunted (LAZ < -2) participated in a randomized controlled trial of micronutrient powder (MNP) in rural India. Following baseline, infants were re-evaluated at 6- and 12-months. **LAZ was calculated from measured length, inflammation (C-reactive protein, CRP) from blood draw; nurturance from home observation (HOME Inventory), and ECD from Mullens Early Learning Scale (visual reception, fine/gross motor and receptive/expressive language).** Linear mixed effects models were conducted, accounting for repeated measures and clustering, adjusted for child age, anemia, maternal education, household assets, and intervention. LAZ interactions with CRP and HOME scores were tested.
Results:
LAZ was significantly positively associated with all ECD domains over time. HOME was positively associated with visual reception and expressive language. HOME interactions were marginal for fine motor ($P = 0.058$) and significant for receptive language ($P = 0.015$). For HOME scores < -1 SD, LAZ was positively related to fine motor and receptive language, for HOME scores >1 SD, LAZ was not related to ECD (Figure 1). CRP was not related to ECD and CRP interaction was not significant.
Conclusions:
The positive association between LAZ and ECD illustrates vulnerability prior to the threshold of stunting. Maternal nurturance is positively associated with multiple domains of infants' ECD and attenuates relations between LAZ and receptive language and fine motor. Inflammation (measured by CRP) is not associated with ECD. **Linear growth within normal and nurturant caregiving are needed to promote ECD.**

Lancet Glob Health. 2019 Mar;7(3):e366-e375. doi: 10.1016/S2214-109X(18)30535-7. (Open access available)

Integrating an early childhood development programme into Bangladeshi primary health-care services: an open-label, cluster-randomised controlled trial.

Hamadani JD, Mehrin SF, Tofail F, Hasan MI, Huda SN, Baker-Henningham H, Ridout D, Grantham-McGregor S.
Bangladesh

BACKGROUND:
Poor development in young children in developing countries is a major problem. Child development experts are calling for interventions that aim to improve child development to be integrated into health services, but there are few robust evaluations of such programmes. Previous small Bangladeshi trials that used individual play sessions with mothers and their children (at home or in clinics), which were predominantly run by employed women, found moderate improvements on childdevelopment. We aimed to **integrate an early childhood development programme into government clinics that provide primary health care and to evaluate the effects of this intervention on child cognition, language, and motor development, growth, and behaviour in a subsample of the children**.

METHODS:
In this open-label cluster-randomised controlled trial, we recruited individuals from community clinics in Narsingdi district, Bangladesh. These clinics were randomly selected from a larger sample of eligible clinics, and they were assigned (1:1) to either **deliver an intervention of 25 sessions, in which mothers of eligible children were shown how to support their child's development through play and interactions, or to deliver no intervention (control group). Participants were underweight children, defined as a weight-for-age Z score of -2 SDs of the WHO standard, who were aged 5-24 months and who lived near the clinic** (defined as a walk of less than 30 min). Government health workers ran these sessions at the clinics as part of their routine work, and mothers and children attended fortnightly in pairs (instead of individual weekly home visits that were specified in the original programme). A subsample of children from each clinic was randomly selected for impact evaluation, and these children were assessed on the Bayley Scales of Infant and Toddler Development for their cognitive, language, and motor performance and for their behaviour with Wolke's ratings, before and after implementation of the intervention. The primary outcomes were the performance of this evaluation subsample on the Bayley and Wolke scales and their anthropometric measurements (weight, length or height, and head circumference) after 1 year of the intervention. This study is registered with ClinicalTrials.gov, number NCT02208531.

FINDINGS:
Between Nov 29, 2014, and April 30, 2015, 12 054 children in 90 clinics were screened, and between six and 25 underweight children were enrolled from each clinic. From the 2423 (20%) underweight children, we excluded 656 (27%) children who lived more than 30-min walking distance from the community clinics, and 30 (1%) children whose mothers did not consent to participate. **We therefore enrolled 1737 (72%) children from these 90 clinics**. **After randomisation, the control group clinics included 878 (51%) children (who all received no intervention) and the intervention group clinics included 859 (49%) children (who all received the child development programme sessions).** Eight children from each clinic (360 [41%] children from the control group clinics and 358 [42%] children from the intervention group clinics) were randomly selected for inclusion in the evaluation subsample. **Between Feb 24, 2016, and Sept 7, 2016, 344 (96%) children in**

control group clinics and 343 (96%) children in intervention group clinics were assessed for the primary outcome. 16 (5%) children in the control group clinics and 15 (4%) children in the intervention group clinics did not provide all data and were not included in final analyses. **An intention-to-treat analysis showed that the intervention significantly improved children's cognition (effect size 1·3 SDs, 95% CI 1·1 to 1·5; p=0·006), language (1·1 SDs, 0·9 to 1·2; p=0·01), and motor composite scores (1·2 SDs, 1·0 to 1·3; p=0·006) and behaviour ratings (ranging from 0·7 SDs, 0·5 to 0·9; p=0·02; to 1·1 SDs, 1·0 to 1·2; p=0·007), but the intervention had no significant effect on growth (p values ranged from 0·05 to 0·74).** Three (1%) children in the intervention group died, but their deaths were not related to the intervention.

INTERPRETATION:
The extent and range of benefits of our intervention are encouraging. Health workers ran most of the sessions effectively and attendance was good, which is promising for scale-up of the intervention model. However, researchers trained and supervised the health workers, and the next step will be to determine whether the Bangladeshi ministry of health can perform these tasks. In future programmes, more attention needs to be paid to the nutrition of the children.

Child Care Health Dev. 2018 Nov;44(6):841-849. doi: 10.1111/cch.12605. Epub 2018 Aug 19.

Prenatal nutrition, stimulation, and exposure to punishment are associated with early child motor, cognitive, language, and socioemotional development in Dar es Salaam, Tanzania.

Pitchik HO, Fawzi WW, McCoy DC, Darling AM, Abioye AI, Tesha F, Smith ER, Mugusi F, Sudfeld CR.
USA, Tanzania

BACKGROUND:
Despite growing evidence that early life experiences and exposures can impact child development, there is limited research on how prenatal and early life nutrition and early life parenting practices predict specific domains of child development in resource-limited settings. This study examines the association between prenatal factors, birth outcomes, and early life characteristics with motor, cognitive/language, and socioemotional development in Tanzania.

METHODS:
We assessed motor, cognitive/language, and socioemotional development among a cohort of 198 children aged 20-39 months in Dar es Salaam, Tanzania, whose mothers were previously enrolled in a randomized, placebo-controlled trial of prenatal vitamin A and zinc supplementation. Linear regression models were used to assess standardized mean differences in child development scores for randomized prenatal regimen and pregnancy, delivery, and early childhood factors.

RESULTS:
Children born to mothers randomized to prenatal vitamin A had significantly lower reported motor scores in minimally adjusted and multivariate analyses, -0.29 SD, 95% CI [-0.54, -0.04], p = 0.03, as compared with children whose mothers did not receive vitamin A. There was no significant effect of randomized prenatal zinc on any development domain. Greater caregiver-child stimulation was associated with 0.38 SD, 95% CI [0.14, 0.63], p < 0.01, better cognitive/language scores, whereas children who experienced both verbal and physical punishment had 0.29 SD, 95% CI [-0.52, -0.05], p = 0.02, lower scores in socioemotional development. Maternal completion of primary school was associated with higher reported motor and cognitive/language development. Further, children of mothers who were <155 cm tall had lower cognitive and language scores.

CONCLUSION:
Prenatal vitamin A supplements in a setting with low levels of vitamin A deficiency may not provide child development benefits. However, integrated environmental, educational, parenting, and stimulation interventions may have large positive effects across child development domains in resource-limited settings.

Soc Sci Med. 2018 Nov;217:32-41. doi: 10.1016/j.socscimed.2018.09.061. Epub 2018 Oct 1.

The effect of affordable daycare on women's mental health: Evidence from a cluster randomized trial in rural India.

Richardson RA, Harper S, Schmitz N, Nandi A.
Canada

Abstract
Access to affordable daycare might improve population mental health. However, evidence is sparse and restricted to middle- and high-income country settings. **We conducted a cluster-randomized controlled trial in one low-income setting, rural Rajasthan, India.** Communities lacking daycare facilities were identified (n = 160) and randomly selected for assistance in setting up a community-based daycare program (n = 80) or not (n = 80). Women eligible for the daycare program living in these communities completed structured interviews before the intervention (participation rate = 89%) and approximately one year after rollout of the intervention (participation rate = 96%), resulting in a final analytic sample of 3041. Mental distress was measured with the Hindi version of the 12-item General Health Questionnaire (score range: 0-12). We modeled the relation between access to daycare and number of mental distress symptoms (GHQ-12 score) with negative binomial regression using an intention-to-treat approach, which groups women according to if they lived in communities randomized to affordable daycare. We also evaluated the effect of access to daycare on secondary outcomes that may be related to mental distress, including women's work burden, agency, and intimate partner violence (IPV). **We found that access to daycare resulted in modest reductions in symptoms of mental distress (mean difference = 0.21, 95% CI: -0.43, 0.02).** We found some evidence that daycare reduced IPV, but virtually no

change in women's work burden or agency. Our results provide some indication that access to affordable daycare might be one policy lever to improve population mental health.

Comment
No Indian authors included

Front Psychol. 2018 Sep 21;9:1751. doi: 10.3389/fpsyg.2018.01751. eCollection 2018. (Open access available)

Effectiveness of a Positive Parental Practices Training Program for Chilean Preschoolers' Families: A Randomized Controlled Trial.

Rincón P, Cova F, Saldivia S, Bustos C, Grandón P, Inostroza C, Streiner D, Bühring V, King M.
Chile, Canada, UK

Abstract
Background: Evidence for the effectiveness of parental training as a strategy for promotion of positive parental practices and prevention of child behavior problems in low and middle income countries is not conclusive. This study aims to assess the effectiveness of a universal positive parental training program designed for this context, "Día a Día" UdeC © ("Day by Day" University of Concepción), in Chilean preschoolers' families (3-6 years old children). **Methods:** A cluster randomized controlled trial (cRCT) was carried out in 19 preschool education centers. **There were two treatment arms: 10 centers (including 178 families) were randomly assigned to the intervention group and nine centers (including 154 families) were assigned to the waiting list control condition.** Intervention groups received Day by Day UdeC, a six group sessions program for parents, including two group sessions for preschool educators, focused in affective communication; daily and child-directed play; directed attention; routines and transitions; reinforcement and incentive programs; planned inattention-ignore and time out; and logical consequences. Parental practices, parental satisfaction, and presence of children behavioral problems were examined at two-time points: T1 (4 weeks before intervention) and T2 (5-6 weeks after intervention). **Results**: Intention-to-treat analysis shows a reduction in physical punishment and an increase in parental involvement, as well as a reduction in children behavioral problems. A per-protocol analysis revealed an additional effect: increase in observed parental practices. **Conclusion:** This cRCT provided evidence for the effectiveness of a parental training program for the promotion of positive parental practices in low and middle income countries. The observed effects of the program in decreasing physical punishment and children's behavioral problems make it a promising strategy for prevention purposes.

Prev Sci. 2018 Oct;19(7):977-986. doi: 10.1007/s11121-018-0941-2.

What Affects Attendance and Engagement in a Parenting Program in South Africa?

Shenderovich Y, Eisner M, Cluver L, Doubt J, Berezin M, Majokweni S, Murray AL.
UK, South Africa, USA

Abstract
Parenting programs are a promising approach to improving family well-being. For families to benefit, programs need to be able to engage families actively in the interventions. Studies in high-income countries show varying results regarding whether more disadvantaged families are equally engaged in parenting interventions. In low- and middle-income countries (LMICs), almost nothing is known about the patterns of participation in parent training. **This paper examines group session attendance and engagement data from 270 high-risk families enrolled in the intervention arm of a cluster-randomized controlled trial in South Africa**. The trial evaluated a 14-week parenting intervention aiming to improve parenting and reduce maltreatment by caregivers. The intervention was delivered in 20 groups, one per study cluster, with 8 to 16 families each. Overall, caregivers attended 50% of group sessions and children, 64%. Using linear multilevel models with Kenward-Roger correction, we examined child and caregiver baseline characteristics as predictors of their attendance and engagement in the group sessions. Variables examined as predictors included measures of economic, educational, and social and health barriers and resources, as well as family problems and sociodemographic characteristics. Overall, the study yielded no evidence that the level of stressors, such as poverty, was related to attendance and engagement. Notably, children from overcrowded households attended on average 1.2 more sessions than their peers. Our findings suggest it is possible to engage highly disadvantaged families that face multiple challenges in parenting interventions in LMICs. However, some barriers such as scheduling, and alcohol and substance use, remain relevant.

PLoS One. 2018 Dec 19;13(12):e0208335. doi: 10.1371/journal.pone.0208335. eCollection 2018. (Open access available)

Effectiveness of a youth-led early childhood care and education programme in rural Pakistan: A cluster-randomised controlled trial.

Yousafzai AK, Rasheed MA, Rizvi A, Shaheen F, Ponguta LA, Reyes CR.
USA, Pakistan

Abstract
BACKGROUND:
The United Nation's Sustainable Development Goals encompass lifelong learning from birth to youth to adulthood (Goal 4) and economic opportunities for young people (Goal 8). The targets include improving access to quality **early childhood care and education (ECCE)** as well as learning and training opportunities for adolescents and youth. Cross-generational models for young children and youth may offer opportunities to address the interconnections between goals and targets for the next generation. We investigated whether an ECCE programme for young children (3.5-6.5 years) delivered by female youth (18-24 years) in rural Pakistan would be effective on children's school readiness.

METHODS:
In partnership with the National Commission for Human Development in Pakistan, we implemented the 'Youth Leaders for Early Childhood Assuring Children are Prepared for

School' (LEAPS) programme to train female youth to deliver ECCE. The effectiveness of the LEAPS programme on children's school readiness was evaluated in a cluster-randomised controlled trial. We randomly allocated five clusters (villages) to receive the intervention (n = 170 children) and five clusters to control (n = 170 children). Children's school readiness was assessed after nine months of intervention exposure using the International Development and Early Learning Assessment tool. Analyses was by intention-to-treat. The trial is registered with ClinicalTrials.gov, number NCT02645162.

FINDINGS:
At endline, the intervention group had significantly higher school readiness scores (n = 166, mean percentage score 59.4, 95% CI 52.7 to 66.2) compared with the control group (n = 168, mean percentage score 45.5, 95% CI 38.8 to 52.3). The effect size (Cohen's d) was 0.3.

CONCLUSION:
Trained female youth delivered an ECCE programme that was effective in benefitting young children's school readiness. The cross-generational model is a promising approach to support early child development; however, further evaluation of the model is needed to assess the specific benefits to youth including their skills and economic development.

PLoS One. 2018 Sep 5;13(9):e0203436. doi: 10.1371/journal.pone.0203436. eCollection 2018. (Open access available)

Effects of schooling on aspects of attention in rural Burkina Faso, West Africa.

Sanou AS, Diallo AH, Holding P, Nankabirwa V, Engebretsen IMS, Ndeezi G, Tumwine JK, Meda N, Tylleskar T, Kashala-Abotnes E.
Norway, Burkina Faso, Kenya, Uganda

BACKGROUND:
We aimed to study the effects of schooling on aspects of attention using the Test of Variables of Attention (TOVA) among children in rural Burkina Faso.

METHODS:
We re-enrolled children of a previously community-based cluster randomized exclusive breastfeeding trial in rural Burkina Faso. A total of 534 children (280 boys and 254 girls) aged 6 to 8 years were assessed using the TOVA. We examined the effect size difference using Cohen's d, ANOVA and conducted regression analyses.

RESULTS:
Forty nine percent of the children were in school. Children not in school performed poorly with a small effect size difference for 'Response Time', 'Errors of omission', and 'Errors of commission' compared to children in school. The effect size difference was moderate for 'Response Time Variability', and 'D prime score'.
CONCLUSION:

Schooling affects different aspects of attention in rural Burkina Faso. In settings where literacy and schooling rate is low, public sensitizations of the benefits of schooling need to be reinforced and advice on sending children to school need to be provided continuously.

Comment
While this aspect was not randomised, the population was taken from within an RCT, and provides very important information on the effects of school on development of attention, which may well not be appreciated if school children are are only tested on correctness of responses.

J Pediatr. 2018 Dec;203:345-353.e3. doi: 10.1016/j.jpeds.2018.07.027. Epub 2018 Aug 29. (Open access available)

Caregiving Disruptions Affect Growth and Pubertal Development in Early Adolescence in Institutionalized and Fostered Romanian Children: A Randomized Clinical Trial.

Johnson DE, Tang A, Almas AN, Degnan KA, McLaughlin KA, Nelson CA, Fox NA, Zeanah CH, Drury SS.
USA, Canada.

OBJECTIVES:
To determine the effects of foster care vs institutional care, as well as disruptions in the caregiving environment on physical development through early adolescence.

STUDY DESIGN:
This was a randomized controlled trial of 114 institutionalized, though otherwise healthy, children from 6 orphanages and 51 never institutionalized control children living in birth families (family care group) in Bucharest, Romania. Children were followed from baseline (21 months, range 5-31) through age 12 years for caregiving disruptions and growth trajectories and through age 14 years for pubertal development.

RESULTS:
Children randomized to the foster care group showed greater rates of growth in height, weight, and body mass index (BMI) through age 12 years than institutionalized group. Tanner development was delayed in institutionalized group boys compared with foster care group and family care group boys at 12 but not 14 years. There were no differences in Tanner development and age of menarche among foster care group, institutionalized group, and family care group girls at ages 12 and 14 years. More disruptions in caregiving between 30 months and 12 years moderated decreases in growth rates of height in foster care group and weight in foster care group and institutionalized group across age. institutionalized group boys with ≥2 disruptions showed lower Tanner scores at age 12 vs institutionalized group and foster care group boys with <2 disruptions. foster care group girls with ≥2 disruptions had higher Tanner scores at age 14 vs foster care group girls with <2 disruptions. Age of menarche was not affected by caregiving disruptions.

CONCLUSIONS:
For children who experienced early institutionalization, stable placement within family care is essential to ensuring the best outcomes for physical developmental.

Comment
No Romanian authors listed.

PLoS One. 2019 Jan 9;14(1):e0209122. doi: 10.1371/journal.pone.0209122. eCollection 2019. (Open access available)

Impact of adversity on early childhood growth & development in rural India: Findings from the early life stress sub-study of the SPRING cluster randomised controlled trial (SPRING-ELS).

Bhopal S, Roy R, Verma D, Kumar D, Avan B, Khan B, Gram L, Sharma K, Amenga-Etego S, Panchal SN, Soremekun S, Divan G, Kirkwood BR.
UK, India, Pakistan, Ghana

INTRODUCTION:
Early childhood development is key to achieving the Sustainable Development Goals and can be negatively influenced by many different adversities including violence in the home, neglect, abuse and parental ill-health. We set out to quantify the extent to which multiple adversities are associated with impaired early childhood growth & development.

METHODS:
This was a substudy of the SPRING **cluster randomised controlled trial covering the whole population of 120 villages of rural India**. We assessed all children born from 18 June 2015 for adversities in the first year of life and summed these to make a total cumulative adversity score, and four subscale scores. We assessed the association of each of these with weight-for-age z-score, length-for-age z-score, and the motor, cognitive and language developmental scales of the Bayley Scales of Infant Development III assessed at 18 months.

RESULTS:
We enrolled 1726 children soon after birth and assessed 1273 of these at both 12 and 18 months of age. There were consistent and strongly negative relationships between all measures of childhood adversity and all five child growth & development outcome measures at 18 months of age. For the Bayley motor scale, each additional adversity was associated with a 1.1 point decrease (95%CI -1.3, -0.9); for the cognitive scales this was 0.8 points (95%CI -1.0, -0.6); and for language this was 1.4 points (95% CI -1.9, -1.1). Similarly for growth, each additional adversity was associated with a -0.09 change in weight-for-age z-score (-0.11, -0.06) and -0.12 change in height-for-age z-score (-0.14, -0.09).

DISCUSSION:
Our results are the first from a large population-based study in a low/middle-income country to show that each increase in adversity in multiple domains increases risk to child growth

and development at a very early age. There is an urgent need to act to improve these outcomes for young children in LMICs and these findings suggest that Early Childhood programmes should prioritise early childhood adversity because of its impact on developmental inequities from the very start.

BMJ Glob Health. 2018 Dec 1;3(6):e001024. doi: 10.1136/bmjgh-2018-001024. eCollection 2018. (Open access available)

Long-term impact of community-based participatory women's groups on child and maternal mortality and child disability: follow-up of a cluster randomised trial in rural Nepal.

Heys M, Gram L, Wade A, Haworth EJN, Osrin D, Sagar K, Shrestha DK, Neupane RP, Adhikari D, Adhikari RK, Budhathoki B, Manandhar D, Costello A.
UK, Nepal

Background:
Community-based women's groups practising participatory learning and action (PLA) can reduce maternal and neonatal mortality in low-income countries. However, **it is not clear whether these reductions are associated with subsequent increased or decreased rates of childhood death and disability.** We assessed the impact on child deaths and disability beyond the perinatal period among participants in the earliest trial in Nepal 2001-2003.

Methods:
Household interviews were conducted with mothers or household heads. At cluster and individual levels, we analysed disability using pairwise log relative risks and survival using multilevel logistic models.

Findings:
From 6075 children and 6117 mothers alive at 4 weeks post partum, 44 419 children (73%) were available for interview a mean 11.5 years later. **Rates of child deaths beyond the perinatal period were 36.6 and 52.0 per 1000 children in the intervention and control arms respectively. Rates of disability were 62.7 and 85.5 per 1000 children in the intervention and control arms respectively. Individual-level analysis, including random effects for cluster pairing and adjusted for baseline maternal literacy, socioeconomic status and maternal age, showed lower, statistically non-significant, odds of child deaths (OR 0.70 (95% CI 0.43 to 1.18) and disability (0.64 (0.39 to 1.06)) in the intervention arm.**

Conclusion:
Community-level exposure to women's groups practising PLA did not significantly impact childhood death or disability or death beyond the perinatal period. Follow-up of other trials with larger sample sizes is warranted in order to explore the possibility of potential long-term survival and disability benefits with greater precision.

J Glob Health. 2019 Jun;9(1):010431. doi: 10.7189/jogh-09-010431. (Open access available)

Child development, growth and microbiota: follow-up of a randomized education trial in Uganda.

Atukunda P, Muhoozi GKM, van den Broek TJ, Kort R, Diep LM, Kaaya AN, Iversen PO, Westerberg AC
Norway, The Netherlands, Uganda, South Africa

Background:
Undernutrition impairs child development outcomes and growth. In this follow-up study of an open cluster-randomized intervention trial we examined the effects of an education package delivered to mothers in rural Uganda on their children's development, growth and gut microbiota at 36 months of age.
Methods:
The parental trial included 511 mother-child pairs recruited when the children were 6-8 months. In that trial, a nutrition, stimulation and hygiene education was delivered to mothers in the intervention group while the control group received routine health care. A follow-up sample of 155 pairs (intervention n = 77, control n = 78) were re-enrolled when the children were 24 months. Developmental outcomes were assessed with the Bayley Scales of Infant and Toddler Development (BSID-III) composite scores for cognitive (primary endpoint), language and motor development. Development outcomes were also evaluated using the Ages and Stages Questionnaire (ASQ) and the Mullen Scales of Early Learning (MSEL). Other outcomes included growth and gut microbiota composition.
Results:
The demographic characteristics were not different ($P > 0.05$) between the intervention and control groups and similar to those of the parental study. The intervention group had higher BSID-III scores than controls, with mean difference 10.13 (95% confidence interval (CI): 3.31-17.05, $P = 0.002$); 7.59 (1.62-13.66, $P = 0.01$); 9.00 (2.92-15.40, $P = 0.005$), for cognitive, language and motor composite scores, respectively. An improvement in the intervention compared to the control group was obtained for both the ASQ and the MSEL scores. The mean difference in height-for-age z-score was higher in the intervention compared to the control group: 0.50 (0.25-0.75, $P = 0.0001$). Gut microbiota composition did not differ significantly between the two study groups.
Conclusions:
The maternal education intervention had positive effects on child development and growth at three years, but did not alter gut microbiota composition. This intervention may be applicable in other low-resource settings.

Diarrhoea

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

Treatment of diarrhoea

S Med. 2019 Jan 24;16(1):e1002734. doi: 10.1371/journal.pmed.1002734. eCollection 2019 Jan. (Open access available)

The role of price and convenience in use of oral rehydration salts to treat child diarrhea: A cluster randomized trial in Uganda.

Wagner Z, Asiimwe JB, Dow WH, Levine DI.
USA, Uganda

BACKGROUND:
Over half a million children die each year of diarrheal illness, although nearly all deaths could be prevented with oral rehydration salts (ORS). The literature on ORS documents both impressive health benefits and persistent underuse. At the same time, little is known about why ORS is underused and what can be done to increase use. We hypothesized that price and inconvenience are important barriers to ORS use and tested whether eliminating financial and access constraints increases ORS coverage.

METHODS AND FINDINGS:
In July of 2016, we recruited **118 community health workers (CHWs; representing 10,384 households) in Central and Eastern Uganda to participate in the study**. Study villages were predominantly peri-urban, and most caretakers had no more than primary school education. In March of 2017, we randomized CHWs to one of four methods of ORS distribution: **(1) free delivery of ORS prior to illness (free and convenient); (2) home sales of ORS prior to illness (convenient only); (3) free ORS upon retrieval using voucher (free only); and (4) status quo CHW distribution, where ORS is sold and not delivered (control).** CHWs offered zinc supplements in addition to ORS in all treatment arms (free in groups 1 and 3 and for sale in group 2), following international treatment guidelines. We used household surveys to measure ORS (primary outcome) and ORS + zinc use 4 weeks after the interventions began (between April and May 2017). We assessed impact using an intention-to-treat (ITT) framework. During follow-up, we identified **2,363 child cases of diarrhea within 4 weeks of the survey (584 in free and convenient [25.6% of households], 527 in convenient only [26.1% of households], 648 in free only [26.8% of households], and 597 in control [28.5% of households]). The share of cases treated with ORS was 77% (448/584) in the free and convenient group, 64% (340/527) in the convenient only group, 74% (447/648) in the free only group, and 56% (335/597) in the control group**. After adjusting for potential confounders, instructing CHWs to provide free and convenient distribution increased ORS coverage by 19 percentage points relative to the control group (95% CI 13-26; P < 0.001), 12 percentage points relative to convenient only (95% CI 6-18; P < 0.001), and 2 percentage points (not significant) relative to free only (95% CI -4 to 8; P = 0.38). Effect sizes were similar, but more pronounced, for the use of both ORS and zinc. Limitations include short follow-up period, self-reported outcomes, and limited generalizability.

CONCLUSIONS:
Most caretakers of children with diarrhea in low-income countries seek care in the private sector where they are required to pay for ORS. However, our results suggest that price is an

important barrier to ORS use and that switching to free distribution by CHWs substantially increases ORS coverage. **Switching to free distribution is low-cost, easily scalable, and could substantially reduce child mortality.** Convenience was not important in this context.

Cochrane Database Syst Rev. 2019 Jan 9;1:CD006085. doi: 10.1002/14651858.CD006085.pub3. (Open access available)

Antiamoebic drugs for treating amoebic colitis.

Gonzales MLM, Dans LF, Sio-Aguilar J.
Philippines

BACKGROUND:
Infection with the protozoan Entamoeba histolytica is common in low- and middle-income countries, and up to 100,000 people with severe disease die every year. Adequate therapy for amoebic colitis is necessary to reduce illness, prevent development of complicated disease and extraintestinal spread, and decrease transmission.

OBJECTIVES:
To evaluate antiamoebic drugs for treating amoebic colitis.

SEARCH METHODS:
We searched the available literature up to 22 March 2018. We searched the Cochrane Infectious Diseases Group Specialised Register, CENTRAL, MEDLINE, Embase, LILACS, mRCT, and conference proceedings. We contacted individual researchers, organizations, and pharmaceutical companies, and we checked reference lists.

SELECTION CRITERIA:
Randomized controlled trials of antiamoebic drugs given alone or in combination, compared with placebo or another antiamoebic drug, for treating adults and children with a diagnosis of amoebic colitis.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed the eligibility and methodological quality of trials and extracted and analysed the data. We calculated clinical and parasitological failure rates and rates of relapse and adverse events as risk ratios (RRs) with 95% confidence intervals (CIs), using a random-effects model. We determined statistical heterogeneity and explored possible sources of heterogeneity using subgroup analyses. We carried out sensitivity analysis by using trial quality to assess the robustness of reported results.

MAIN RESULTS:
In total, 41 trials (4999 participants) met the inclusion criteria of this review. In this update, we added four trials to the 37 trials included in the first published review version. Thirty trials were published over 20 years ago. Only one trial used adequate methods of randomization and allocation concealment, was blinded, and analysed all randomized participants. Only one trial used an E histolytica stool antigen test, and two trials used amoebic

culture.**Tinidazole may be more effective than metronidazole for reducing clinical failure (RR 0.28, 95% CI 0.15 to 0.51; 477 participants, eight trials; low-certainty evidence) and is probably associated with fewer adverse events (RR 0.65, 95% CI 0.46 to 0.92; 477 participants, 8 trials; moderate-certainty evidence).** Compared with metronidazole, combination therapy may result in fewer parasitological failures (RR 0.36, 95% CI 0.15 to 0.86; 720 participants, 3 trials; low-certainty evidence), but we are uncertain which combination is more effective than another. Evidence is insufficient to allow conclusions regarding the efficacy of other antiamoebic drugs.

AUTHORS' CONCLUSIONS:
Compared with metronidazole, tinidazole may be more effective in reducing clinical failure and may be associated with fewer adverse events. Combination drug therapy may be more effective for reducing parasitological failure compared with metronidazole alone. However, these results are based mostly on small trials conducted over 20 years ago with a variety of poorly defined outcomes. Tests that detect E histolytica more accurately are needed, particularly in countries where concomitant infection with other bacteria and parasites is common.

Diarrhoea prevention

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

Trials. 2018 Jul 31;19(1):412. doi: 10.1186/s13063-018-2797-y. (Open access available)

The effect of SODIS water treatment intervention at the household level in reducing diarrheal incidence among children under 5 years of age: a cluster randomized controlled trial in Dabat district, northwest Ethiopia.

Bitew BD, Gete YK, Biks GA, Adafrie TT.
Ethiopia

BACKGROUND:
Solar Disinfection (SODIS) of water is an economical, user-friendly, and environmentally safe household water treatment method that has been advocated as a means of decreasing the burden of diarrhea among children under 5 years of age. Laboratory studies have consistently shown the efficacy of the SODIS method to destroy waterborne pathogens. However, the evidence-based health effect of a SODIS intervention at the household level is limited. The main aim of the study was to examine the effectiveness of a SODIS intervention in reducing the incidence of diarrhea among under-five children.

METHODS:
A community-based, cluster randomized controlled trial was conducted, over 6 months from 10 January to 7 July 2016, in 28 rural villages of northwest Ethiopia. **In the intervention group, 384 children in 279 households received polyethylene terephthalate (PET) bottles, and in the control group 394 children in 289 households who continued to use their usual drinking-water sources were included in the trial.** The study compared

diarrheal incidence among the intervention group children who were exposed to SODIS household water treatment and the control group children who were not exposed to such water treatment. A generalized estimating equation (GEE) model was used to compute the adjusted incidence rate ratio and the corresponding 95% confidence interval.

RESULTS:
In this trial, the overall SODIS compliance was 90.6%. The incidence of diarrhea was 8.3 episodes/100 person-week observations in the intervention group compared to 15.3 episodes/100 person-week observations in the control group. A statistically significant reduction was observed in the incidence of diarrhea in the intervention group compared to the control (adjusted IRR 0.60 (95% CI 0.52, 0.70) with a corresponding prevention of 40% (95% CI: 34, 48).

CONCLUSION:
The SODIS intervention substantially reduced the incidence of diarrhea among under-five children in a rural community of northwest Ethiopia. This indicates that a SODIS intervention is an invaluable strategy that needs to be integrated with the National Health Extension Program to be addressed to rural communities.

Cochrane Database Syst Rev. 2018 Dec 17;12:CD011654. doi: 10.1002/14651858.CD011654.pub2. (Open access available)

Fly control to prevent diarrhoea in children.

Das JK, Hadi YB, Salam RA, Hoda M, Lassi ZS, Bhutta ZA.
Pakistan

BACKGROUND:
Diarrhoeal disease accounts for millions of child deaths every year. Although the role of flies as vectors of infectious diarrhoea has been established, fly control is not often mentioned as an approach to decrease childhood diarrhoea. Theoretically, fly control for decreasing diarrhoea incidence can be achieved by intervening at four different levels: reduction or elimination of fly breeding sites; reduction of sources that attract houseflies; prevention of contact between flies and disease-causing organisms; and protection of people, food, and food utensils from contact with flies.

OBJECTIVES:
To assess the impact of various housefly control measures on the incidence of diarrhoea and its related morbidity and mortality in children under five years of age.

SEARCH METHODS:
We searched electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, CINAHL, and LILACS, from database inception to 24 May 2018. We also searched trial registries for relevant grey literature and ongoing trials. We checked the references of the identified studies and

reviews. We did not apply any filters for language, publication status (published, unpublished, in press, and ongoing), or publication date.

SELECTION CRITERIA:
We planned to include randomized controlled trials (RCTs), quasi-RCTs, and controlled before-and-after studies that studied the effect of fly control on diarrhoea in children under five years of age.

DATA COLLECTION AND ANALYSIS:
Two review authors extracted the data and independently assessed the risk of bias in the included study. We planned to contact study authors for additional information, where necessary. We assessed the certainty of the evidence using the GRADE approach.

MAIN RESULTS:
We included one cluster-RCT (491 participants) conducted in Pakistan that evaluated insecticide spraying in the first two years and baited fly traps in the third year. Insecticide spraying reduced the fly population (house index) in the intervention group during the four months of the year when both flies and cases of diarrhoea were more common, but not at other times. On average, this was associated with a reduction in the incidence of diarrhoea in the first year (illustrative mean episodes per child-year in the intervention group was 6.3 while in the control group was 7.1) and second year of the intervention (illustrative mean episodes per child–year in the intervention group was 4.4 while in the control group was 6.5; rate ratio (RaR) 0.77, 95% confidence interval (CI) 0.67 to 0.89, low-certainty evidence). In the third year of the intervention, the baited fly traps did not demonstrate an effect on the fly population or on diarrhoea incidence (RaR 1.15, 95% CI 0.90 to 1.47, low-certainty evidence).

AUTHORS' CONCLUSIONS:
The trial, conducted in a setting where there were clear seasonal peaks in fly numbers and associated diarrhoea, shows insecticide spraying may reduce diarrhoea in children. Further research on whether this finding is applicable to other setting is required, as well as work on other fly control methods, their effects, feasibility, costs, and acceptability.

Ear disease and hearing loss

Einstein (Sao Paulo). 2019 Mar 7;17(2):eAO4423. doi: 10.31744/einstein_journal/2019AO4423. (Open access available)

Water protection in patients with tympanostomy tubes in tympanic membrane: a randomized clinical trial.

Miyake MM, Tateno DA, Cançado NA, Miyake MM, Tincani S, Sousa Neto OM.
Brazil

OBJECTIVE:

To analyze the incidence of otorrhea in the postoperative period of patients submitted to tympanotomy to place ventilation tube, and who did not protect the ear when exposed to water.

METHODS:
Open, randomized-controlled trial. Eighty patients submitted to unilateral or bilateral ear grommet tympanostomy were included and divided into two groups: Auricular Protection and Non-Protection to water during bathing and activities in water.

RESULTS:
In the first postoperative month, the Non-Protection Group presented a significant increase in the number of patients with otorrhea and in the incidence. Four patients of the Protection Group (11%) presented at least one episode of otorrhea in this period, representing an incidence of 0.11 (standard deviation ±0.32) episode/month, whereas in the Non-Protection Group there were 12 episodes (33%; p=0.045) and incidence of 0.33 (±0.48; p=0.02). Between the 2nd and the 13th postoperative months, there was no difference between groups. Seven patients in the Protection Group (20%) had at least one episode of otorrhea, representing an incidence of 0.04 (±0.09) episodes/month, while in the Non-Protection Group there were seven episodes (22%; p=0.8) and incidence of 0.05 (±0.1; p=0.8).

CONCLUSION:
Patients who underwent ear protection when exposed to water had a lower incidence of otorrhea in the first postoperative month than those who did not undergo protection. From the second month, there was no difference between groups.

BMC Pediatr. 2019 May 23;19(1):163. doi: 10.1186/s12887-019-1539-y.

Effect of a participatory intervention in women's self-help groups for the prevention of chronic suppurative otitis media in their children in Jumla Nepal: a cluster-randomised trial.

Clarke S[1], Richmond R[2], Worth H[2], Wagle R[3], Hayen A[4].
Australia, Nepal

BACKGROUND:
Chronic suppurative otitis media (CSOM) causes preventable deafness and disproportionately affects children living in poverty. Our hypothesis was that health promotion in women's groups would increase their knowledge, attitudes and practices (KAP) regarding ear disease and reduce the prevalence of CSOM in their children.
METHODS:
We did a cluster randomised trial in two village development committees (VDCs) in Jumla, Nepal. In July 2014, 30 women's groups were randomly allocated to intervention or control, stratified by VDC and distance to the road. The intervention groups participated in three sessions of health promotion using the WHO Hearing and Ear Care Training Resource Basic Level. The primary outcome was women's KAP score and the secondary outcome was prevalence of CSOM in their children at 12 month follow-up. Analyses were by intention to treat. Participants and the research team were not masked to allocation.

RESULTS:
In June and July 2014 we recruited 508 women and 937 of their children. 12 months later there was no difference in the women's KAP score (mean difference 0.14, 95% CI - 0.1 to 0.38, P = 0.25) or the prevalence of CSOM in their children (OR 1.10, 95%CI 0.62 to 1.84, P = 0.75) between intervention and control groups. However, overall, there was a significant improvement in the KAP score (mean difference - 0.51, 95% CI - 0.71,to - 0.31, P < 0.0001) and in the prevalence of CSOM from baseline 11.2% to follow-up 7.1% (P < 0.0001).
CONCLUSIONS:
Health promotion in women's groups did not improve maternal KAP or reduce prevalence of CSOM. Over time there was a significant improvement in women's KAP score and reduction in the prevalence of CSOM which may be attributable to our presence in the community offering treatment to affected children, talking to their parents and providing ciprofloxacin drops to the local health posts. More research is needed in low resource settings to test our findings.

Ebola and viral haemorrhagic fever

Endocrine disorders and bone health

Diabetes

Bone health

Indian J Endocrinol Metab. 2018 Nov-Dec;22(6):760-765. doi: 10.4103/ijem.IJEM_84_18.
(Open access available)
Efficacy and Safety of 90,000 IU versus 300,000 IU Single Dose Oral Vitamin D in Nutritional Rickets: A Randomized Controlled Trial.
Mittal M, Yadav V, Khadgawat R, Kumar M, Sherwani P.
India

AIM:
To compare efficacy and safety of 90,000 IU versus 300,000 IU oral single dose vitamin D for treatment of nutritional rickets.

STUDY DESIGN:
Randomized controlled trial.

SETTING:
Tertiary care hospital.

PARTICIPANTS:

One hundred ten children (6 months to 5 years, median age 10.5 months) with rickets. Exclusion criteria were disease affecting absorption, intake of calcium/vitamin D preparation in last 6 months, abnormal renal function, and rickets other than nutritional.

INTERVENTION:
Vitamin D3 as a single oral dose 90,000 IU (group A, *n* = 55) or 300,000 IU (group B, *n*= 55).

METHODOLOGY:
Severity of rickets was scored on knee and wrist X-ray as per Thacher's radiographic score. Baseline serum levels of calcium, SAP, 25(OH)D, iPTH were measured. Follow up was done at 1 week, 4 weeks, and 12 weeks.

OUTCOME VARIABLE:
Primary - Radiographic score at 3 months. Secondary - Serum levels of 25(OH)D, SAP, and iPTH at 3 months, clinical and biochemical adverse effects.

RESULTS:
Eighty-six subjects (43 in each group) completed the study. The radiographic score reduced from 6.90 to 0.16 in group A and from 6.93 to 0.23 in group B. The levels of 25(OH)D, ALP, and PTH were similar between the groups at baseline and follow up. Hypercalciuria and hypercalcemia were seen more often in group B as was hypervitaminosis D. There were no clinical adverse events.

CONCLUSIONS:
Single oral dose vitamin D3 90,000 IU is safe and effective in achieving healing of rickets.

Epilepsy and acute seizures

Mymensingh Med J. 2018 Oct;27(4):776-784.

A Randomized Controlled Trial of Phenobarbital and Levetiracetam in Childhood Epilepsy.

Akter N, Rahman MM, Akhter S, Fatema K.
Bangladesh

Abstract
Levetiracetam has been introduced for the control of seizures besides phenobarbital as monotherapy in children with epilepsy. This study was aimed to compare the effectiveness of these two drugs for the control of seizures in epilepsy. This randomized controlled trial was done to assess the **efficacy and tolerability of levetiracetam compared to phenobarbital in childhood epilepsy** and was conducted in Institute of Pediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh among **children between 1 month to 15 years who were diagnosed as cases of epilepsy** (idiopathic focal, generalized, focal with secondary generalization)

according to ILAE to assess the effect of Levetiracetam (n=50) and Phenobarbital (n=68) from May 2015 to July 2016. The children were followed up for 12 months at 3 months interval to compare the seizure remission and side effects of Levetiracetam and Phenobarbital. **The children in levetiracetam group was about 10 months older along with older age of onset of seizure (p=0.02) than those of phenobarbital group (p=0.03 and 0.02 respectively).** GTCS was the most common type of seizure in both groups. **During 3 months of intervention 55.8% patients of levetiracetam group achieved 50-75% seizure remission compared to 44.2% in phenobarbital group, at 6 months period 75-100% seizure remission observed among 57.4% patients of levetiracetam group compared to 42.6% of phenobarbital group (p=0.06), which continued to increase at 9 months in levetiracetam (n=33, 55.9%) compared to phenobarbital (n=26, 44.1%) and this value is statistically significant (p=0.05).** No further improvement observed at 12 months follow up. Behavioral problem was reported among 4 patients of phenobarbital group without any evidence of cognitive deterioration, only 3 patients of levetiracetam experienced irritability, but no children of both group discontinued treatment due to side effects. Levetiracetam mono-therapy is more effective in controlling seizures in focal, generalized and focal with secondary generalization epilepsy compared to phenobarbital with minimum side effects.

J Pediatr Neurosci. 2018 Apr-Jun;13(2):158-164. doi: 10.4103/jpn.JPN_126_17. (Open access available)

IV Levetiracetam versus IV Phenytoin in Childhood Seizures: A Randomized Controlled Trial.

Singh K, Aggarwal A, Faridi MMA, Sharma S.
India

Objectives:
To compare the efficacy of IV phenytoin and IV levetiracetam in acute seizures.

Design:
Randomized controlled trial.

Setting:
Tertiary care hospital, November 2012 to April 2014.

Patients:
100 children aged 3-12 yrs of age presenting with acute seizures.

Intervention:
Participants randomly received either IV phenytoin 20 mg/kg (*n* = 50) or IV levetiracetam 30 mg/kg (*n* = 50). Patients who were had seizures at presentation received IV diazepam prior to these drugs.

Outcome Measures:

Primary: Absence of seizure activity within next 24 hrs.*Secondary:* Stopping of clinical seizure activity within 20 mins of first intervention, change in cardiorespiratory parameters, and achievement of therapeutic drug levels.

Results:
Two groups were comparable in patient characteristics and seizure type ($P > 0.05$). Of the 100 children, 3 in levetiracetam and 2 in phenytoin group had a repeat seizure in 24 hrs, efficacy was comparable (94% vs 96%, $P > 0.05$). Of these, 18 (36%) in phenytoin and 12 (24%) in levetiracetam group received diazepam. Sedation time was 178.80 ±97.534 mins in phenytoin and 145.50 ±105.208 mins in levetiracetam group ($P = 0.346$). Changes in cardiorespiratory parameters were similar in both groups except a lower diastolic blood pressure with phenytoin ($P = 0.023$). Therapeutic drug levels were achieved in 38 (76%) children both at 4 and 24 hrs with phenytoin, compared to 50 (100%) and 48 (98%) at 1 and 24 hrs with levetiracetam ($P < 0.05$).

Conclusion:
Intravenous levetiracetam and phenytoin have similar efficacy in preventing seizure recurrences for 24 hrs in children 3-12 years presenting with acute seizures.

Nutr ESPEN. 2019 Feb;29:36-40. doi: 10.1016/j.clnesp.2018.11.007. Epub 2018 Nov 23.

Effect of high dose vitamin d supplementation on vitamin D nutrition status of pre-pubertal children on anti-epileptic drugs - A randomized controlled trial.

Viraraghavan VR, Seth A, Aneja S, Singh R, Dhanwal D.
India

BACKGROUND AND AIMS:
Patients on long term anti-epileptic drug therapy are prone for Vitamin D deficiency for a myriad of reasons. The aim of this research was to study the effect of high dose vitamin D supplementation on vitamin D nutrition status of children newly started on anti-epileptic drug therapy.

MATERIALS:
This randomized controlled trial was conducted in a tertiary care Children's Hospital at New Delhi from November 2011 to March 2013. **Eighty three children in the age group 5-10 years newly started on anti-epileptic drugs (AED) were randomized into two groups; group A - the intervention group, to whom 60,000 IU vitamin D3 was given orally/month under direct supervision along with AED for a period of 6 months, and group B- the control group, to whom AED without vitamin D3 was given**. Serum 25(OH)D, ionized calcium (iCa), total calcium (tCa), inorganic phosphate (iP), alkaline phosphatase (ALP) and parathyroid hormone (PTH) levels were assayed at baseline and at the end of 6 months and were compared within and between the two groups.

RESULTS:
The mean 25(OH)D in Group A was maintained at 6 months follow up [26 ng/ml, 95% CI 20-34 ng/ml] compared to baseline [25 ng/ml, 95% CI -19 to 33 ng/ml] [p = 0.83]. In group B, there was a significant decrease in 25(OH)D levels at 6 months [13 ng/ml (95% CI 9 ng/ml-17 ng/ml)] compared to baseline [18 ng/ml (95% CI 13-24 ng/ml)] [p = 0.01]. At 6 months, mean serum 25(OH)D was significantly higher in group A as compared to group B (p = 0.005).

CONCLUSION:
To conclude, oral administration of 60,000 IU vitamin D3/month is sufficient to maintain serum 25(OH)D level and prevent development of vitamin D deficiency in children newly started on AED over a period of 6 months. Non supplementation leads to the lowering of serum 25(OH)D in these children.

Epilepsy Behav. 2019 Mar;92:191-194. doi: 10.1016/j.yebeh.2018.11.038. Epub 2019 Jan 23.

Impact of structured teaching program on the parent's knowledge of domiciliary management of seizure-A randomized controlled trial.

Kumar R, Khakha DC, Gulati S, Kaushik JS.
India

Abstract
The aim of study was to assess the combined effectiveness of structured teaching program (STP) and patient information pamphlet (PIS) on caregivers' knowledge with regard to domiciliary management of seizure as compared with PIS alone. Study participants included caregivers of typically developing children aged 1-18 years with at least one episode of convulsion. The enrolled participants were allocated to either of the two groups: intervention group (STP along with PIS) and control group (PIS). The outcome was measured by a structured questionnaire - 'first-aid measures knowledge questionnaire'. Baseline knowledge scores were recorded and compared with postintervention scores measured at one-month follow-up. The preintervention knowledge scores were comparable in the two groups (p = 0.72). The control group has shown no significant difference in the knowledge scores at one-month follow-up (p = 0.58). Postintervention knowledge scores (p < 0.01) and mean difference in the knowledge scores (p < 0.01) were significantly higher in the intervention group when compared with controls. Structured teaching program regarding first-aid measures for convulsion along with PIS was effective in improving the knowledge of caregivers than PIS alone.

PLoS Negl Trop Dis. 2019 Jan 24;13(1):e0007101. doi: 10.1371/journal.pntd.0007101. eCollection 2019 Jan. (Open access available)

Estimating the association between being seropositive for cysticercosis and the prevalence of epilepsy and severe chronic headaches in 60 villages of rural Burkina Faso.

Sahlu I, Carabin H, Ganaba R, Preux PM, Cissé AK, Tarnagda Z, Gabriël S, Dermauw V, Dorny P, Bauer C, Millogo A.
USA, Burkina Faso, Canada, France, Belgium

BACKGROUND:
Individuals diagnosed with **neurocysticercosis often present with epilepsy and sometimes with progressively worsening severe chronic headaches (WSCH).** While cross-sectional associations between seropositivity to cysticercal antigens and epilepsy have been reported, few large scale studies have been conducted in West Africa and none have measured the association between seropositivity to cysticercal antigens and headaches. This study aimed at filling these knowledge gaps by estimating the strength of the cross-sectional association between seropositivity to cysticercal antigens and the prevalence of epilepsy and WSCH in 60 villages of Burkina Faso, West Africa.

METHODOLOGY/PRINCIPAL FINDINGS:
Baseline data from a cluster randomized controlled trial collected from January 2011 to February 2012 in 60 villages across three provinces in Burkina Faso were used. **Between 78 and 80 individuals were screened for epilepsy and WSCH in each village, and those screened positive were confirmed by a physician.** Seventy-five percent of all participants were asked to provide a blood sample to test for Taenia solium cysticercus circulating antigens. Hierarchical multivariable logistic models were used to measure the association between seropositivity to cysticercal antigens and epilepsy (lifetime and active) as well as WSCH. Among 3696 individuals who provided a blood sample, 145 were found to have epilepsy only, 140 WSCH only and 19 both. **There were positive associations between seropositivity to cysticercal antigens and active epilepsy (prevalence odds ratio (POR): 2.40 (95%CI: 1.15-5.00)) and WSCH (POR: 2.59 (1.34-4.99)).**

CONCLUSIONS/SIGNIFICANCE:
Our study is the first to demonstrate a cross-sectional association between seropositivity to cysticercal antigens and WSCH in a large community-based study conducted in West Africa. The measured cross-sectional association had a strength similar to the ones previously observed between seropositivity to cysticercal antigens and lifetime or active epilepsy. As a result, preventing new cysticercosis cases in communities may reduce the prevalence of these two important neurological disorders.

Epilepsia Open. 2019 Mar 6;4(2):264-274. doi: 10.1002/epi4.12311. eCollection 2019 Jun.

A home-based, primary-care model for epilepsy care in India: Basis and design.

Singh G, Sharma S, Bansal RK, Setia RK, Sharma S, Bansal N, Chowdhury A, Goraya JS, Chatterjee S, Kaur S, Kaur M, Kalra S, Sander JW
India, UK, The Netherlands.

Objectives:

A cluster-randomized trial of home-based care using primary-care resources for people with epilepsy has been set up to optimize epilepsy care in resource-limited communities in low- and middle-income countries. The primary aim is to determine whether treatment adherence to antiepileptic drugs is better with home-based care or with routine clinic-based care. The secondary aims are to compare the effects of the two care pathways on seizure control and quality of life.
Methods:
The home-based intervention comprises epilepsy medication provision, adherence reinforcement, and epilepsy self-management and stigma management guidance provided by an auxiliary nurse-midwife equivalent. The experimental group will be compared to a routine clinic-based care group using a cluster-randomized design in which the unit of analysis is a cluster of 10 people with epilepsy residing in an area cared for by a single accredited government grass-roots health care worker. The primary outcome is treatment adherence as measured by monthly tablet counts supplemented by two self-completed questionnaires. The secondary outcomes include monthly seizure frequency, time to first seizure (in days) after enrollment, proportion of patients experiencing seizure freedom for the duration of the study, and quality of life measured by the "Personal Impact of Epilepsy Scale," all assessed by an independent study nurse.
Results:
The screening phase and neurologic evaluations and randomizations have been recently completed and follow-up is underway.
Significance:
The results of the trial are likely to have substantial bearing on the development of governmental policies and strategies to provide coverage and care for patients with epilepsy in resource-limited countries.

J Pediatr Neurosci. 2018 Oct-Dec;13(4):410-415. doi: 10.4103/JPN.JPN_88_18. (Open access available)

Yoga in Children with Epilepsy: A Randomized Controlled Trial.

Kanhere SV, Bagadia DR, Phadke VD, Mukherjee PS.
India

CONTEXT:
Majority of epilepsy begins in childhood. Twenty to thirty percent of patients may not respond to antiepileptic drugs. Yoga as a complementary therapy has been found to be beneficial in adults, but has not yet been studied in children with epilepsy.

AIM:
To study the effect of yoga on seizure and electroencephalogram (EEG) outcome in children with epilepsy.

SETTING AND DESIGN:

A randomized controlled trial was conducted in the pediatric neurology outpatient department of a tertiary care teaching hospital.

MATERIALS AND METHODS:
Twenty children aged 8-12 years with an unequivocal diagnosis of epilepsy on regular antiepileptic drugs were enrolled. Yoga therapy was provided to 10 children (study group) and 10 children formed the control group. Yoga therapy was given as 10 sessions of 1h each. We compared seizure frequency and EEG at baseline, 3, and 6 months. Statistical analysis was carried out using standard statistical tests. A *P* value of <0.05 was considered significant.

RESULTS:
No children had seizures at the end of 3 and 6 months in the study group. In the control group, at 3 and 6 months, four and three children, respectively, had seizures.
Eight children each in both the groups had an abnormal EEG at enrollment. At the end of 6 months, one EEG in the study group and seven in the control group were abnormal (*P* = 0.020).

CONCLUSION:
Yoga as an additional therapy in children with epilepsy leads to seizure freedom and significant improvement in EEG at 6 months.

Comment
A Cochrane review (2017) concluded: No reliable evidence to support the use of yoga as a treatment for control of epilepsy, in view of methodological deficiencies such as limited number of studies, limited number of participants randomised to yoga, lack of blinding and limited data on quality-of-life outcome.

Eur J Paediatr Neurol. 2019 Jan;23(1):136-142. doi: 10.1016/j.ejpn.2018.09.006. Epub 2018 Sep 22.

Safety, tolerability, and effectiveness of oral zonisamide therapy in comparison with intramuscular adrenocorticotropic hormone therapy in infants with West syndrome.

Angappan D, Sahu JK, Malhi P, Singhi P.
India

Abstract
West syndrome is a distinct, infantile onset, epileptic encephalopathy, associated with poor neurodevelopmental outcome. The present study was designed as a randomized, open-label, pilot study to evaluate the **safety, feasibility, and effectiveness of oral zonisamide therapy in comparison with adrenocorticotropic hormone therapy in infants with West syndrome**. **Thirty infants with West syndrome were randomized to receive treatment with either synthetic, intramuscular adrenocorticotropic hormone (30-60 IU) or oral zonisamide (4-25 mg/kg/day).** The study participants had a long treatment lag and preponderance of male sex (90%). The primary effectiveness outcome measure was the cessation of epileptic spasms at 2 weeks of initiation of therapy and persistent till 6 weeks as

per West Delphi consensus statement recommendations. **Comparison of efficacies of zonisamide versus adrenocorticotropic hormone was as following: the cessation of epileptic spasms (27% vs. 40%, p = 0.70), resolution of hypsarrhythmia at 14 days (20% vs. 33%, p = 0.68) and resolution of hypsarrhythmia at 6 weeks (36% vs. 71%, p = 0.14).** Overall, the study observed a poor efficacy of both adrenocorticotropic hormone and zonisamide therapy, which is probably due to long treatment lag and a high proportion of structural aetiology. However, oral zonisamide appeared to be safe and tolerable in the study.

Economics, equity and poverty alleviation

J Policy Anal Manage. 2018 Summer;37(3):602-629. doi: 10.1002/pam.22065. Epub 2018 May 29.

Effects of Financial Incentives on Saving Outcomes and Material Well-Being: Evidence From a Randomized Controlled Trial in Uganda.

Wang JS, Ssewamala FM, Neilands TB, Bermudez LG, Garfinkel I, Waldfogel J, Brooks-Gunn J, You J.

Hong Kong, USA, China

Abstract

The use of savings products to promote financial inclusion has increasingly become a policy priority across sub-Saharan Africa, yet little is known about how families respond to varying levels of savings incentives and whether the promotion of incentivized savings in low-resource settings may encourage households to restrict expenditures on basic needs. Using data from a randomized controlled trial in Uganda, we examine: 1) whether low-income households enrolled in an economic-empowerment intervention consisting of matched savings, workshops, and mentorship reduced spending on basic needs and 2) how varied levels of matching contributions affected household savings and consumption behavior. **We compared primary school-attending AIDS-affected children (N = 1,383) randomized to a control condition with two intervention arms with differing savings-match incentives: 1:1 (Bridges) and 1:2 (Bridges PLUS)**. We found that: 1) 24 months post-intervention initiation, children in Bridges and Bridges PLUS were more likely to have accumulated savings than children in the control condition; 2) higher match incentives (Bridges PLUS) led to higher deposit frequency but not higher savings in the bank; 3) intervention participation did not result in material hardship; and 4) in both intervention arms, participating families were more likely to start a family business and diversify their assets.

BMC Pregnancy Childbirth. 2019 Jan 16;19(1):32. doi: 10.1186/s12884-019-2172-3. (Open access available)

Conditional cash transfers to prevent mother-to-child transmission in low facility-delivery settings: evidence from a randomised controlled trial in Nigeria.

Liu JX, Shen J, Wilson N, Janumpalli S, Stadler P, Padian N.
USA

Abstract
BACKGROUND:
Nigeria suffers from the highest burden of mother-to-child transmission worldwide. To increase retention in care and prevention programmes, we piloted and evaluated a conditional cash transfer (CCT) programme for preventing mother-to-child transmission (PMTCT) in Akwa Ibom, Nigeria.

METHODS:
In a randomised controlled trial, pregnant women testing positive for HIV during antenatal care registration at three public hospitals were randomised to one of two study arms: (1) offered enrolment into the CCT programme or (2) continue in standard care for (PMTCT). In the CCT programme, women could receive a compensation package totaling 33,300 Naira (~US$114) for enroling, delivering at the facility, and obtaining a newborn early infant diagnosis (EID) test. The intent-to-treat (ITT) and per protocol (PP) effects of the programme on the primary outcomes of facility delivery and EID testing and on the secondary outcome of nevirapine administration were estimated with logistic regressions.

RESULTS:
From August 1, 2015 to April 19, 2017, 554 pregnant women tested positive for HIV; 273 were randomised to standard care and 281 were offered enrolment into the CCT intervention. **Women offered the CCT programme were more likely to give birth at the facility (n = 109/263; 41.4%) compared to women in standard care (n = 80/254; 31.5%), an absolute difference of 9.9% (OR = 1.54, 95% CI: 1.07-2.21, p = 0.019).** For EID testing there was an absolute difference of 12.8% between those offered the CCT intervention (n = 69/263; 26.2%) and those in standard care (n = 34/254; 13.4%; OR = 2.30, 95% CI 1.46-3.62, p = 0.000). PP results show larger differences for both facility deliveries (16.7% absolute difference; OR = 2.02, 95% CI 1.38-2.98, p = 0.000) and EID testing (18.9% absolute difference; OR = 3.09, 95% CI 1.93-4.94, p = 0.000) among intervention enrolees. Over 86% of the facility-delivered newborns received nevirapine, and ITT and PP estimates were similar to those for facility deliveries.

CONCLUSIONS:
Results show that CCTs improved the likelihood of HIV-positive women giving birth at a facility, of nevirapine being administered to their newborn, and of undergoing EID testing in Akwa Ibom, Nigeria. Effects are especially large among those who agreed to participate in the CCT intervention.

Comment
No author from Nigeria included

J Health Econ. 2019 Feb 18;65:15-30. doi: 10.1016/j.jhealeco.2018.12.001. [Epub ahead of print] (Open access available)

Cash on delivery: Results of a randomized experiment to promote maternal health care in Kenya.

Grépin KA, Habyarimana J, Jack W.
Kenya

Abstract
We conducted a randomized controlled experiment to test whether vouchers, cash transfers, and SMS messages were effective in boosting facility delivery rates among poor, pregnant women in rural Kenya. We find a strong effect of the full vouchers and the conditional cash transfers: 48% of women with access to both interventions delivered in a health facility, while only 36% of those with neither did. Amongst women who did not receive a cash transfer, we find that a small copayment dramatically reduced voucher effectiveness, suggesting a discontinuous impact of cost-sharing on the demand for health services. Both the unconditional cash transfer and the text messages had limited effect on the use of health services. Finally, we also find no evidence that a government policy to eliminate user fees increased demand for maternal health services.

PLoS Med. 2018 Oct 29;15(10):e1002684. doi: 10.1371/journal.pmed.1002684. eCollection 2018 Oct. (Open access available)

A cash-based intervention and the risk of acute malnutrition in children aged 6-59 months living in internally displaced persons camps in Mogadishu, Somalia: A non-randomised cluster trial.

Grijalva-Eternod CS, Jelle M, Haghparast-Bidgoli H, Colbourn T, Golden K, King S, Cox CL, Morrison J, Skordis-Worrall J, Fottrell E, Seal AJ.
UK, Ireland, Kenya

Abstract
BACKGROUND:
Somalia has been affected by conflict since 1991, with children aged <5 years presenting a high acute malnutrition prevalence. Cash-based interventions (CBIs) have been used in this context since 2011, despite sparse evidence of their nutritional impact. We aimed to understand whether a CBI would reduce acute malnutrition and its risk factors.

METHODS AND FINDINGS:
We implemented a non-randomised cluster trial in internally displaced person (IDP) camps, located in peri-urban Mogadishu, Somalia. Within 10 IDP camps (henceforth clusters) selected using a humanitarian vulnerability assessment, all households were targeted for the CBI. Ten additional clusters located adjacent to the intervention clusters were selected as controls. The CBI comprised a monthly unconditional cash transfer of US$84.00 for 5 months, a once-only distribution of a non-food-items kit, and the provision of piped water free of charge. The cash transfers started in May 2016. Cash recipients were female household representatives. In March and September 2016, from a cohort of randomly selected households in the intervention (n = 111) and control (n = 117) arms (household cohort), we collected household and individual level data from children aged 6-59 months (155 in the

intervention and 177 in the control arms) and their mothers/primary carers, to measure known malnutrition risk factors. In addition, between June and November 2016, data to assess acute malnutrition incidence were collected monthly from a cohort of children aged 6-59 months, exhaustively sampled from the intervention (n = 759) and control (n = 1,379) arms (child cohort). Primary outcomes were the mean Child Dietary Diversity Score in the household cohort and the incidence of first episode of acute malnutrition in the child cohort, defined by a mid-upper arm circumference < 12.5 cm and/or oedema. Analyses were by intention-to-treat. For the household cohort we assessed differences-in-differences, for the child cohort we used Cox proportional hazards ratios. In the household cohort, the CBI appeared to increase the Child Dietary Diversity Score by 0.53 (95% CI 0.01; 1.05). In the child cohort, the acute malnutrition incidence rate (cases/100 child-months) was 0.77 (95% CI 0.70; 1.21) and 0.92 (95% CI 0.53; 1.14) in intervention and control arms, respectively. The CBI did not appear to reduce the risk of acute malnutrition: unadjusted hazard ratio 0.83 (95% CI 0.48; 1.42) and hazard ratio adjusted for age and sex 0.94 (95% CI 0.51; 1.74). The CBI appeared to increase the monthly household expenditure by US$29.60 (95% CI 3.51; 55.68), increase the household Food Consumption Score by 14.8 (95% CI 4.83; 24.8), and decrease the Reduced Coping Strategies Index by 11.6 (95% CI 17.5; 5.96). The study limitations were as follows: the study was not randomised, insecurity in the field limited the household cohort sample size and collection of other anthropometric measurements in the child cohort, the humanitarian vulnerability assessment data used to allocate the intervention were not available for analysis, food market data were not available to aid results interpretation, and the malnutrition incidence observed was lower than expected.

CONCLUSIONS:
The CBI appeared to improve beneficiaries' wealth and food security but did not appear to reduce acute malnutrition risk in IDP camp children. Further studies are needed to assess whether changing this intervention, e.g., including specific nutritious foods or social and behaviour change communication, would improve its nutritional impact.

Fever

Am J Trop Med Hyg. 2018 Nov;99(5):1255-1261. doi: 10.4269/ajtmh.17-0777. (Open access available)

Management and Follow-up Practices of Children with Unclassified Fever in Rural Ethiopia: Experiences of Health Extension Workers and Caregivers.

Funk T, Källander K, Abebe A, Hailemariam A, Alvesson HM, Alfvén T.
Sweden, UK, Ethiopia

Abstract
Different health-care management guidelines by the World Health Organization exist to help health workers in resource-limited settings treat patients. However, for children with unclassified fever and no danger signs, management guidelines are less clear and follow-up

recommendations differ. Both a "universal follow-up" for all children, irrespective of health status, and a "conditional follow-up" only for children whose fever persists are recommended in different guidelines. It is unclear how feasible and acceptable these two different follow-up guidelines are among community health workers and caregivers of the sick child. This qualitative study was conducted in Ethiopia and was nested within a cluster-randomized controlled trial (cRCT). It aimed to determine health extension workers' (HEWs') and caregivers' experiences of the management of febrile children and their perceptions of universal versus conditional follow-up recommendations. Seventeen HEWs and 20 caregivers were interviewed. **The interviews revealed that HEWs' understanding of how to handle an unclassified fever diagnosis increased with the implementation of the cRCT in both study arms (universal versus conditional follow-up). This enabled HEWs to withhold medicines from children with this condition and avoid referral to health centers**. Both follow-up recommendations had perceived advantages, while the universal follow-up provided an opportunity to see the child's health progress, the conditional follow-up advice allowed saving time and costs. The findings suggest that improved awareness of the unclassified fever condition can make HEWs feel more comfortable in managing these febrile children themselves and omitting unnecessary medication. Future community-level management guidelines should provide clearer instructions on managing fever where no malaria, pneumonia, diarrhea, or danger signs are present.

Fluid management

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Isotonic versus hypotonic saline as maintenance intravenous fluid therapy in children under 5 years of age admitted to general paediatric wards: a randomised controlled trial.

Kumar M, Mitra K, Jain R.
India.

Background: To prevent the risk of iatrogenic hyponatraemia in hospitalised children, isotonic fluid has been recommended as maintenance intravenous fluid (IVF). There are few studies which compare half normal saline with normal saline as maintenance IVF in general paediatric wards. **Aim**: To compare the safety and efficacy of half normal saline with normal saline as maintenance IVF in general paediatric wards. **Methods**: Children aged between 3 months and 5 years with an anticipated requirement for IVF for 24 h were **randomised to receive either half normal saline (0.45% saline in 5% dextrose) or normal saline (0.9% saline in 5% dextrose).** The primary objective was to compare the incidence of hyponatraemia (serum sodium <135 mmol/L with a decrease from baseline of at least 4 mmol/L) at 24 h in children receiving half normal saline with those receiving normal saline. Secondary objectives were to compare the incidence of moderate (sodium <130 mmol/L), severe (sodium <125 mmol/L) and symptomatic hyponatraemia, change in serum sodium level from baseline and the incidence of hypernatraemia. **Results**: A total of **168 children were randomised to receive either normal saline (*n* = 84) or half normal saline (*n* = 84).** More than two-thirds of the children were suffering from respiratory diseases (pneumonia

and bronchiolitis) and diseases of the nervous system (meningoencephalitis, febrile seizures and epilepsy). **The incidence of hyponatraemia at 12 h in children receiving half normal saline was similar to that in those receiving normal saline (6 *vs* 4.8%; Relative risk (RR) 1.2; 95% CI 0.3.0-4.8; *p* = 0.73). Although the incidence of hyponatraemia at 24 h in children receiving half normal saline was higher than in those receiving normal saline, the difference was not statistically significant (14.3 *vs* 6%; RR 2.6; 95% CI 0.9-7.8; *p* = 0.07**). One child in the isotonic group and one in the hypotonic group developed moderate and severe hyponatraemia, respectively. There was no significant difference in the incidence of hypernatraemia between two groups (RR 0.7; 95% CI 0.16-3.3). **Conclusion**: Half-normal saline as maintenance IVF does not result in a significantly increased risk of hyponatraemia in general paediatric ward patients under 5 years of age.

Health promotion

BMJ Glob Health. 2018 Jul 16;3(4):e000808. doi: 10.1136/bmjgh-2018-000808. eCollection 2018. (Open access available)

Modelling the effect of a mass radio campaign on child mortality using facility utilisation data and the Lives Saved Tool (LiST): findings from a cluster randomised trial in Burkina Faso.

Murray J, Head R, Sarrassat S, Hollowell J, Remes P, Lavoie M, Borghi J, Kasteng F, Meda N, Badolo H, Ouedraogo M, Bambara R, Cousens S.

UK, Burkina Faso

Background:
A cluster randomised trial (CRT) in Burkina Faso was the first to demonstrate that a radio campaign increased health-seeking behaviours, specifically antenatal care attendance, health facility deliveries and primary care consultations for children under 5 years.

Methods:
Under-five consultation data by diagnosis was obtained from primary health facilities in trial clusters, from January 2011 to December 2014. Interrupted time-series analyses were conducted to assess the intervention effect by time period on under-five consultations for separate diagnosis categories that were targeted by the media campaign. The Lives Saved Tool was used to estimate the number of under-five lives saved and the per cent reduction in child mortality that might have resulted from increased health service utilisation. Scenarios were generated to estimate the effect of the intervention in the CRT study areas, as well as a national scale-up in Burkina Faso and future scale-up scenarios for national media campaigns in five African countries from 2018 to 2020.

Results:
Consultations for malaria symptoms increased by 56% in the first year (95% CI 30% to 88%; p<0.001) of the campaign, 37% in the second year (95% CI 12% to 69%; p=0.003) and 35% in the third year (95% CI 9% to 67%; p=0.006) relative to the increase in the control arm. Consultations for lower respiratory infections increased by 39% in the first year of the campaign (95% CI 22% to 58%; p<0.001), 25% in the second (95% CI 5% to 49%; p=0.010) and

11% in the third year (95% CI -20% to 54%; p=0.525). Diarrhoea consultations increased by 73% in the first year (95% CI 42% to 110%; p<0.001), 60% in the second (95% CI 12% to 129%; p=0.010) and 107% in the third year (95% CI 43% to 200%; p<0.001). Consultations for other diagnoses that were not targeted by the radio campaign did not differ between intervention and control arms. The estimated reduction in under-five mortality attributable to the radio intervention was 9.7% in the first year (uncertainty range: 5.1%-15.1%), 5.7% in the second year and 5.5% in the third year. The estimated number of under-five lives saved in the intervention zones during the trial was 2967 (range: 1110-5741). If scaled up nationally, the estimated reduction in under-five mortality would have been similar (9.2% in year 1, 5.6% in year 2 and 5.5% in year 3), equating to 14 888 under-five lives saved (range: 4832-30 432). The estimated number of lives that could be saved by implementing national media campaigns in other low-income settings ranged from 7205 in Burundi to 21 443 in Mozambique.

Conclusion:
Evidence from a CRT shows that a child health radio campaign increased under-five consultations at primary health centres for malaria, pneumonia and diarrhoea (the leading causes of postneonatal child mortality in Burkina Faso) and resulted in an estimated 7.1% average reduction in under-five mortality per year. These findings suggest important reductions in under-five mortality can be achieved by mass media alone, particularly when conducted at national scale.

Comment
This modelling paper may overstate the case, given the original Burkina Faso trial did not show a reduction in child mortality. This metrhod and approach was highly contested https://gh.bmj.com/content/bmjgh/3/5/e001194.full.pdf and https://gh.bmj.com/content/bmjgh/3/5/e001222.full.pdf

BMJ Glob Health. 2018 Jul 16;3(4):e000809. doi: 10.1136/bmjgh-2018-000809. eCollection 2018. (Open access available)

Cost-effectiveness and economies of scale of a mass radio campaign to promote household life-saving practices in Burkina Faso.

Kasteng F, Murray J, Cousens S, Sarrassat S, Steel J, Meda N, Ouedraogo M, Head R, Borghi J.
Author information
UK, Burkina Faso

Introduction:
Child health promotion through mass media has not been rigorously evaluated for cost-effectiveness in low-income and middle-income countries. We assessed the cost-effectiveness of a mass radio campaign on health-seeking behaviours for child survival within a trial in Burkina Faso and at national scale.

Methods:

We collected provider cost data prospectively alongside a 35-month cluster randomised trial in rural Burkina Faso in 2012-2015. Out-of-pocket costs of care-seeking were estimated through a household survey. We modelled intervention effects on child survival based on increased care-seeking and estimated the intervention's incremental cost-effectiveness ratio (ICER) in terms of the cost per disability-adjusted life year (DALY) averted versus current practice. Model uncertainty was gauged using one-way and probabilistic sensitivity analyses. We projected the ICER of national-scale implementation in five sub-Saharan countries with differing media structures. All costs are in 2015 USD.

Results:
The provider cost of the campaign was $7 749 128 ($9 146 101 including household costs). The campaign broadcast radio spots 74 480 times and 4610 2-hour shows through seven local radio stations, reaching approximately 2.4 million people including 620 000 direct beneficiaries (pregnant women and children under five). It resulted in an average estimated 24% increase in care-seeking for children under five and a 7% reduction in child mortality per year. The ICER was estimated at $94 ($111 including household costs (95% CI -38 to 320)). The projected provider cost per DALY averted of a national level campaign in Burkina Faso, Burundi, Malawi, Mozambique and Niger in 2018-2020, varied between $7 in Malawi to $27 in Burundi.

Conclusion:
This study suggests that mass-media campaigns can be very cost-effective in improving child survival in areas with high media penetration and can potentially benefit from considerable economies of scale.

Hygiene, sanitation and environmental health

Indoor air pollution

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Effects of a large-scale distribution of water filters and natural draft rocket-style cookstoves on diarrhea and acute respiratory infection: A cluster-randomized controlled trial in Western Province, Rwanda.

Kirby MA, Nagel CL, Rosa G, Zambrano LD, Musafiri S, Ngirabega JD, Thomas EA, Clasen T
United Kingdom, United States of America, Rwanda, Tanzania

BACKGROUND:
Unsafe drinking water and household air pollution (HAP) are major causes of morbidity and mortality among children under 5 in low and middle-income countries. Household water filters and higher-efficiency biomass-burning cookstoves have been widely promoted to

improve water quality and reduce fuel use, but there is limited evidence of their health effects when delivered programmatically at scale.

METHODS AND FINDINGS:

In a large-scale program in Western Province, Rwanda, water filters and portable biomass-burning natural draft rocket-style cookstoves were distributed between September and December 2014 and promoted to over 101,000 households in the poorest economic quartile in 72 (of 96) randomly selected sectors in Western Province. To assess the effects of the intervention, between August and December, 2014, we enrolled **1,582 households that included a child under 4 years from 174 randomly selected village-sized clusters, half from intervention sectors and half from nonintervention sectors**. At baseline, 76% of households relied primarily on an improved source for drinking water (piped, borehole, protected spring/well, or rainwater) and over 99% cooked primarily on traditional biomass-burning stoves. **We conducted follow-up at 3 time-points between February 2015 and March 2016 to assess reported diarrhea and acute respiratory infections (ARIs) among children <5 years in the preceding 7 days (primary outcomes) and patterns of intervention use, drinking water quality, and air quality**. **The intervention reduced the prevalence of reported child diarrhea by 29% (prevalence ratio [PR] 0.71, 95% confidence interval [CI] 0.59-0.87, p = 0.001) and reported child ARI by 25% (PR 0.75, 95% CI 0.60-0.93, p = 0.009).** Overall, more than 62% of households were observed to have water in their filters at follow-up, while 65% reported using the intervention stove every day, and 55% reported using it primarily outdoors. Use of both the intervention filter and intervention stove decreased throughout follow-up, while reported traditional stove use increased. **The intervention reduced the prevalence of households with detectable fecal contamination in drinking water samples by 38% (PR 0.62, 95% CI 0.57-0.68, p < 0.0001) but had no significant impact on 48-hour personal exposure to log-transformed fine particulate matter (PM2.5) concentrations among cooks (β = -0.089, p = 0.486) or children (β = -0.228, p = 0.127).** The main limitations of this trial include the unblinded nature of the intervention, limited PM2.5 exposure measurement, and a reliance on reported intervention use and reported health outcomes.

CONCLUSIONS:

Our findings indicate that the intervention improved household drinking water quality and reduced caregiver-reported diarrhea among children <5 years. It also reduced caregiver-reported ARI despite no evidence of improved air quality. Further research is necessary to ascertain longer-term intervention use and benefits and to explore the potential synergistic effects between diarrhea and ARI.

Water, Sanitation and Hygiene

Lancet Glob Health. 2019 Jan;7(1):e132-e147. doi: 10.1016/S2214-109X(18)30374-7. (Open access available)

Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial.

Humphrey JH, Mbuya MNN, Ntozini R, Moulton LH, Stoltzfus RJ, Tavengwa NV, Mutasa K, Majo F, Mutasa B, Mangwadu G, Chasokela CM, Chigumira A, Chasekwa B, Smith LE, Tielsch JM, Jones AD, Manges AR, Maluccio JA, Prendergast AJ; Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial Team.

BACKGROUND:
Child stunting reduces survival and impairs neurodevelopment. We tested the independent and combined effects of improved water, sanitation, and hygiene (WASH), and improved infant and young child feeding (IYCF) on stunting and anaemia in in Zimbabwe.

METHODS:
We did a cluster-randomised, community-based, 2 × 2 factorial trial in two rural districts in Zimbabwe. Clusters were defined as the catchment area of between one and four village health workers employed by the Zimbabwe Ministry of Health and Child Care. Women were eligible for inclusion if they permanently lived in clusters and were confirmed pregnant. Clusters were randomly assigned (1:1:1:1) to standard of care (52 clusters), IYCF (20 g of a small-quantity lipid-based nutrient supplement per day from age 6 to 18 months plus complementary feeding counselling; 53 clusters), WASH (construction of a ventilated improved pit latrine, provision of two handwashing stations, liquid soap, chlorine, and play space plus hygiene counselling; 53 clusters), or IYCF plus WASH (53 clusters). A constrained randomisation technique was used to achieve balance across the groups for 14 variables related to geography, demography, water access, and community-level sanitation coverage. Masking of participants and fieldworkers was not possible. The primary outcomes were infant length-for-age Z score and haemoglobin concentrations at 18 months of age among children born to mothers who were HIV negative during pregnancy. These outcomes were analysed in the intention-to-treat population. We estimated the effects of the interventions by comparing the two IYCF groups with the two non-IYCF groups and the two WASH groups with the two non-WASH groups, except for outcomes that had an important statistical interaction between the interventions. This trial is registered with ClinicalTrials.gov, number NCT01824940.

FINDINGS:
Between Nov 22, 2012, and March 27, 2015, 5280 pregnant women were enrolled from 211 clusters. 3686 children born to HIV-negative mothers were assessed at age 18 months (**884 in the standard of care group from 52 clusters, 893 in the IYCF group from 53 clusters, 918 in the WASH group from 53 clusters, and 991 in the IYCF plus WASH group from 51 clusters**). In the IYCF intervention groups, the mean length-for-age Z score was 0·16 (95% CI 0·08-0·23) higher and the mean haemoglobin concentration was 2·03 g/L (1·28-2·79) higher than those in the non-IYCF intervention groups. **The IYCF intervention reduced the number of stunted children from 620 (35%) of 1792 to 514 (27%) of 1879, and the number of children with anaemia from 245 (13·9%) of 1759 to 193 (10·5%) of 1845. The WASH intervention had no effect on either primary outcome.** Neither intervention reduced the prevalence of diarrhoea at 12 or 18 months. No trial-related serious adverse events, and only three trial-related adverse events, were reported.

INTERPRETATION:

Household-level elementary WASH interventions implemented in rural areas in low-income countries are unlikely to reduce stunting or anaemia and might not reduce diarrhoea. Implementation of these WASH interventions in combination with IYCF interventions is unlikely to reduce stunting or anaemia more than implementation of IYCF alone.

PLoS Med. 2019 Mar 21;16(3):e1002766. doi: 10.1371/journal.pmed.1002766. eCollection 2019 Mar. (Open access available)

Independent and combined effects of improved water, sanitation, and hygiene (WASH) and improved complementary feeding on early neurodevelopment among children born to HIV-negative mothers in rural Zimbabwe: Substudy of a cluster-randomized trial.

Gladstone MJ, Chandna J, Kandawasvika G, Ntozini R, Majo FD, Tavengwa NV, Mbuya MNN, Mangwadu GT, Chigumira A, Chasokela CM, Moulton LH, Stoltzfus RJ, Humphrey JH, Prendergast AJ; SHINE Trial Team.

Abstract
BACKGROUND:
Globally, nearly 250 million children (43% of all children under 5 years of age) are at risk of compromised neurodevelopment due to poverty, stunting, and lack of stimulation. We tested the independent and combined effects of improved water, sanitation, and hygiene (WASH) and improved infant and young child feeding (IYCF) on early child development (ECD) among children enrolled in the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial in rural Zimbabwe.

METHODS AND FINDINGS:
SHINE was a cluster-randomized community-based 2×2 factorial trial. A total of 5,280 pregnant women were enrolled from 211 clusters (defined as the catchment area of 1-4 village health workers [VHWs] employed by the Zimbabwean Ministry of Health and Child Care). **Clusters were randomly allocated to standard of care, IYCF (20 g of small-quantity lipid-based nutrient supplement per day from age 6 to 18 months plus complementary feeding counseling), WASH (ventilated improved pit latrine, handwashing stations, chlorine, liquid soap, and play yard), and WASH + IYCF.** Primary outcomes were child length-for-age Z-score and hemoglobin concentration at 18 months of age. Children who completed the 18-month visit and turned 2 years (102-112 weeks) between March 1, 2016, and April 30, 2017, were eligible for the ECD substudy. We prespecified that primary inferences would be drawn from findings of children born to HIV-negative mothers; these results are presented in this paper. A total of 1,655 HIV-unexposed children (64% of those eligible) were recruited into the ECD substudy from 206 clusters and evaluated for ECD at 2 years of age using the Malawi Developmental Assessment Tool (MDAT) to assess gross motor, fine motor, language, and social skills; the MacArthur-Bates Communicative Development Inventories (CDI) to assess vocabulary and grammar; the A-not-B test to assess object permanence; and a self-control task. Outcomes were analyzed

in the intention-to-treat population. For all ECD outcomes, there was not a statistical interaction between the IYCF and WASH interventions, so we estimated the effects of the interventions by comparing the 2 IYCF groupswith the 2 non-IYCF groups and the 2 WASH groups with the 2 non-WASH groups. The mean (95% CI) total MDAT score was modestly higher in the IYCF groups compared to the non-IYCF groups in unadjusted analysis: 1.35 (0.24, 2.46; p = 0.017); this difference did not persist in adjusted analysis: 0.79 (-0.22, 1.68; p = 0.057). There was no evidence of impact of the IYCF intervention on the CDI, A-not-B, or self-control tests. Among children in the WASH groups compared to those in the non-WASH groups, mean scores were not different for the MDAT, A-not-B, or self-control tests; mean CDI score was not different in unadjusted analysis (0.99 [95% CI -1.18, 3.17]) but was higher in children in the WASH groups in adjusted analysis (1.81 [0.01, 3.61]). The main limitation of the study was the specific time window for substudy recruitment, meaning not all children from the main trial were enrolled.

CONCLUSIONS:
We found little evidence that the IYCF and WASH interventions implemented in SHINE caused clinically important improvements in child development at 2 years of age. Interventions that directly target neurodevelopment (e.g., early stimulation) or that more comprehensively address the multifactorial nature of neurodevelopment may be required to support healthy development of vulnerable children.

BMJ Glob Health. 2019 Jan 5;4(1):e000973. doi: 10.1136/bmjgh-2018- 000973. eCollection 2019. (Open access available)

Can child-focused sanitation and nutrition programming improve health practices and outcomes? Evidence from a randomised controlled trial in Kitui County, Kenya.

Gimaiyo G, McManus J, Yarri M, Singh S, Trevett A, Moloney G, Robins A, Lehmann L.
Kenya, Uganda, UNICEF, Philippines

Introduction:
In Kenya's Kitui County, 46% of children under 5 years are stunted. Sanitation and nutrition programmes have sought to reduce child undernutrition, though they are typically implemented separately. We evaluate the effectiveness of an **integrated sanitation and nutrition (SanNut)** intervention in improving caregiver sanitation and nutrition knowledge and behaviours.

Methods:
We conducted a cluster-randomised controlled trial to evaluate the impact of the SanNut intervention on caregiver knowledge, sanitary and hygiene practices, sanitation outcomes and nutrition outcomes. The evaluation included caregivers of children under 5 years across 604 villages in Kitui County. **309 treatment villages were randomly assigned to receive both the SanNut intervention and the standard Community-Led Total Sanitation (CLTS) intervention, while 295 control villages only received the CLTS intervention**. 8

households with children under 5 years were randomly selected from each evaluation village to participate in the endline survey, for a total of 4322 households.

Results:
SanNut led to modest improvements in sanitary knowledge and practices emphasised by the programme. Caregivers in treatment villages were 3.3 pp (+32%) more likely to mention lack of handwashing after handling child faeces as a potential cause of diarrhoea, and 4.9 pp (+7.8%) more likely to report safe disposal of child faeces than caregivers in control villages. Treatment households were 1.9 pp (+79%) more likely to have a stocked handwashing station and 2.9 pp (-16%) less likely to report incidences of child diarrhoea. However, SanNut appears to have had no impact on nutritional practices, such as breastfeeding, vitamin A supplementation or deworming. Non-child outcomes traditionally associated with CLTS, including latrine use and homestead sanitary conditions, were similar in treatment and control groups.

Conclusion:
Child-focused messaging can potentially be integrated into CLTS programming, though this integration was more successful for topics closer to CLTS objectives (sanitation practices, including limiting faecal contamination and handwashing) than for more disparate topics (nutritional practices).

Trials. 2018 Jul 6;19(1):358. doi: 10.1186/s13063-018-2710-8. (Open access available)

Achieving optimal technology and behavioral uptake of single and combined interventions of water, sanitation hygiene and nutrition, in an efficacy trial (WASH benefits) in rural Bangladesh.

Parvez SM, Azad R, Rahman M, Unicomb L, Ram PK, Naser AM, Stewart CP, Jannat K, Rahman MJ, Leontsini E, Winch PJ, Luby SP.
Bangladesh, USA

BACKGROUND:
Uptake matters for evaluating the health impact of water, sanitation and hygiene (WASH) interventions. Many large-scale WASH interventions have been plagued by low uptake. For the WASH Benefits Bangladesh efficacy trial, high uptake was a prerequisite. We assessed the degree of technology and behavioral uptake among participants in the trial, as part of a three-paper series on WASH Benefits Intervention Delivery and Performance.

METHODS:
This study is a cluster randomized trial comprised of geographically matched clusters among four districts in rural Bangladesh. **We randomly allocated 720 clusters of 5551 pregnant women to individual or combined water, sanitation, handwashing, and nutrition interventions, or a control group. Behavioral objectives included; drinking chlorine-treated, safely stored water; use of a hygienic latrine and safe feces disposal at the compound level; handwashing with soap at key times; and age-appropriate nutrition**

behaviors (pregnancy to 24 months) including a lipid-based nutrition supplement (LNS). Enabling technologies and behavior change were promoted by trained local community health workers through periodic household visits. To monitor technology and behavioral uptake, we conducted surveys and spot checks in 30-35 households per intervention arm per month, over a 20-month period, and structured observations in 324 intervention and 108 control households, approximately 15 months after interventions commenced.

RESULTS:
In the sanitation arms, observed adult use of a hygienic latrine was high (94-97% of events) while child sanitation practices were moderate (37-54%). In the handwashing arms, handwashing with soap was more common after toilet use (67-74%) than nonintervention arms (18-40%), and after cleaning a child's anus (61-72%), but was still low before food handling. In the water intervention arms, more than 65% of mothers and index children were observed drinking chlorine-treated water from a safe container. Reported LNS feeding was > 80% in nutrition arms. There was little difference in uptake between single and combined intervention arms.

CONCLUSIONS:
Rigorous implementation of interventions deployed at large scale in the context of an efficacy trial achieved high levels of technology and behavioral uptake in individual and combined WASH and nutrition intervention households. Further work should assess how to achieve similar uptake levels under programmatic conditions.

Trials. 2018 Jul 6;19(1):359. doi: 10.1186/s13063-018-2709-1. (Open access available)

WASH Benefits Bangladesh trial: management structure for achieving high coverage in an efficacy trial.

Unicomb L, Begum F, Leontsini E, Rahman M, Ashraf S, Naser AM, Nizame FA, Jannat K, Hussain F, Parvez SM, Arman S, Mobashara M, Luby SP, Winch PJ.
Bangladesh, USA

BACKGROUND:
Water, sanitation, and hygiene (WASH) efficacy trials deliver interventions to the target population under optimal conditions to estimate their effects on outcomes of interest, to inform subsequent selection for inclusion in routine programs. A systematic and intensive approach to intervention delivery is required to achieve the high-level uptake necessary to measure efficacy. We describe the intervention delivery system adopted in the WASH Benefits Bangladesh study, as part of a three-paper series on WASH Benefits Intervention Delivery and Performance.

METHODS:
Community Health Workers (CHWs) delivered individual and combined WASH and nutrition interventions to 4169 enrolled households in geographically matched clusters. Households were provided with free enabling technologies and supplies, integrated with parallel behaviour-change promotion. Behavioural objectives were drinking treated, safely stored

water, safe feces disposal, handwashing with soap at key times, and age-appropriate nutrition behaviours (birth to 24 months). The intervention delivery system built on lessons learned from prior WASH intervention effectiveness, implementation, and formative research studies. We recruited local CHWs, residents of the study villages, through transparent merit-based selection methods, and consultation with community leaders. CHW supervisors received training on direct intervention delivery, then trained their assigned CHWs. CHWs in turn used the technologies in their own homes. Each CHW counseled six to eight intervention households spread across a 0.2-2.2-km radius, with a 1:12 supervisor-to-CHW ratio. CHWs met monthly with supervisor-trainers to exchange experiences and adapt technology and behaviour-change approaches to evolving conditions. Intervention uptake was tracked through fidelity measures, with a priori benchmarks necessary for an efficacy study.

RESULTS:
Sufficient levels of uptake were attained by the fourth intervention assessment month and sustained throughout the intervention period. Periodic internal CHW monitoring resulted in discontinuation of a small number of low performers.

CONCLUSIONS:
The intensive intervention delivery system required for an efficacy trial differs in many respects from the system for a routine program. To implement a routine program at scale requires further research on how to optimize the supervisor-to-CHW-to-intervention household ratios, as well as other program costs without compromising program effectiveness.

Trials. 2018 Jul 6;19(1):360. doi: 10.1186/s13063-018-2708-2. (Open access available)

WASH Benefits Bangladesh trial: system for monitoring coverage and quality in an efficacy trial.

Rahman M, Ashraf S, Unicomb L, Mainuddin AKM, Parvez SM, Begum F, Das KK, Naser AM, Hussain F, Clasen T, Luby SP, Leontsini E, Winch PJ.
Bangladesh, USA

BACKGROUND:
Researchers typically report more on the impact of public health interventions and less on the degree to which interventions were followed implementation fidelity. We developed and measured fidelity indicators for the WASH Benefits Bangladesh study, a large-scale efficacy trial, in order to identify gaps between intended and actual implementation.

METHODS:
Community health workers (CHWs) delivered individual and combined water, sanitation, handwashing (WSH) and child nutrition interventions to 4169 enrolled households in geographically matched clusters. Households received free enabling technologies (insulated water storage container; sani-scoop, potty, double-pit, pour-flush latrine; handwashing station, soapy-water storage bottle), and supplies (chlorine tablets, lipid-based nutrient

supplements, laundry detergent sachets) integrated with parallel behavior-change promotion. Behavioral objectives were drinking treated, safely stored water, safe feces disposal, handwashing with soap at key times, and age-appropriate nutrition behaviors. We administered monthly surveys and spot-checks to households from randomly selected clusters for 6 months early in the trial. If any fidelity measures fell below set benchmarks, a rapid response mechanism was triggered.

RESULTS:
In the first 3 months, functional water seals were detected in 33% (14/42) of latrines in the sanitation only arm; 35% (14/40) for the combined WSH arm; and 60% (34/57) for the combined WSH and Nutrition arm, all falling below the pre-set benchmark of 80%. Other fidelity indicators met the 65 to 80% uptake benchmarks. Rapid qualitative investigations determined that households concurrently used their own latrines with broken water seals in parallel with those provided by the trial. In consultation with the households, we closed pre-existing latrines without water seals, increased the CHWs' visit frequency to encourage correct maintenance of latrines with water seals, and discouraged water-seal removal or breakage. At the sixth assessment, 86% (51/59) of households were in sanitation only; 92% (72/78) in the combined WSH; and 93% (71/76) in the combined WSH and Nutrition arms had latrines with functional water seals.

CONCLUSIONS:
An intensive implementation fidelity monitoring and rapid response system proved beneficial for this efficacy trial. To implement a routine program at scale requires further research into an adaptation of fidelity monitoring that supports program effectiveness.

J Dev Econ. 2019 May;138:1-16. doi: 10.1016/j.jdeveco.2018.12.001. (Open access available)

Scaling up sanitation: Evidence from an RCT in Indonesia.

Cameron L, Olivia S, Shah M.
Australia, New Zealand, USA

Abstract
We investigate the impacts of a widely used sanitation intervention, Community-Led Total Sanitation, which was implemented at scale across rural areas of Indonesia with a randomized controlled trial to evaluate its effectiveness. The program resulted in modest increases in toilet construction, decreased community tolerance of open defecation and reduced roundworm infestations in children. However, there was no impact on anemia, height or weight. We find important heterogeneity along three dimensions: (1) poverty-poorer households are limited in their ability to improve sanitation; (2) implementer identity-scale up involves local governments taking over implementation from World Bank contractors yet no sanitation and health benefits accrue in villages with local government implementation; and (3) initial levels of social capital-villages with high initial social capital built toilets whereas the community-led approach was counterproductive in low social capital villages with fewer toilets being built.

Comment
No author from Indonesia included

Hand hygiene to prevent newborn infection

BMC Public Health. 2018 Nov 20;18(1):1279. doi: 10.1186/s12889-018-6201-3. (Open access available)

Preventing neonatal sepsis in rural Uganda: a cross-over study comparing the tolerance and acceptability of three alcohol-based hand rub formulations.

Ditai J, Mudoola M, Gladstone M, Abeso J, Dusabe-Richards J, Adengo M, Olupot-Olupot P, Carrol ED, Storr J, Medina-Lara A, Faragher B, Weeks AD.
Author information
Uganda, UK, Switzerland, WHO

Abstract
BACKGROUND:
Neonatal sepsis causes 0.5 million deaths annually, mostly in low resource settings. Babies born in African rural homes without running water or toilet facilities are especially vulnerable. **Alcohol-based hand rub (ABHR) may be used by mothers and carers as an alternative to hand washing with soap to prevent neonatal infection.** However, no definite study has established the preferred formulation of hand rub for the mothers. This study aimed to assess the effects of addition of bitterants and perfume towards the acceptability of the alcohol-based hand rubs by the mothers in their homes after childbirth.

METHODS:
This was a 3-way blinded cross-over study design. Mothers with children aged ≤3 months were recruited from immunisation clinics at 3 local health facilities in rural eastern Uganda and received 3-different ABHR formulations (in the order plain, bitterant and perfumed) packed in 100 ml bottles. Each ABHR was used for 5 consecutive days followed by a 2-day 'washout' period (evaluation period). Overall satisfaction with each hand rub was evaluated at the end of each week using a 7-point Likert scale.

RESULTS:
A total of 43 women were recruited, whose ages ranged from 16 to 45 years (mean 26.2 years old). None of the participants normally used a hand protective lotion/cream. The three formulations were used for a mean of 5 (range 3-7) days. **A significantly greater volume of the "bitterant" and "perfumed" formulations (mean 91 and 83 ml respectively) were used in comparison to the "plain" formulation (mean 64 ml).** Overall satisfaction was high with all the hand rubs, but the perfumed formulation had a significantly higher overall satisfaction score [mean 6.7, range 4-7] compared with the plain [6.4, 3-7] and bitterant [6.2, 2-7] formulations.

CONCLUSIONS:
All the 3 ABHR formulations were well accepted with little to choose between them. The ABHR with added perfume scored highest on overall satisfaction and was used significantly more often than plain ABHR. ABHR with bitterant additive did, however, score highly and may be a preferable choice to those with concern over alcohol misuse.

Pilot Feasibility Stud. 2019 Mar 26;5:49. doi: 10.1186/s40814-019-0432-7. eCollection 2019. (Open access available)

BabyGel pilot: a pilot cluster randomised trial of the provision of alcohol handgel to postpartum mothers to prevent neonatal and young infant infection-related morbidity in the community.

Ditai J, Abeso J, Odeke NM, Mobbs N, Dusabe-Richards J, Mudoola M, Carrol ED, Olupot-Olupot P, Storr J, Medina-Lara A, Gladstone M, Faragher EB, Weeks AD.
Uganda

BACKGROUND:
Alcohol-based hand rub (ABHR) is widely used in both health and social facilities to prevent infection, but it is not known whether supplying it for regular perinatal use can prevent newborn sepsis in African rural homes. Our study piloted a cluster randomised trial of providing ABHR to postpartum mothers to prevent neonatal infection-related morbidity in the communities.

METHODS:
We conducted a pilot parallel cluster randomised controlled trial across ten villages (clusters) in rural Eastern Uganda. Pregnant women of over 34 weeks' gestation were recruited over a period of 3 months. **Both clusters received the standard of care of antenatal health education, Maama Kit, and clinic appointments. In addition, women in the intervention villages received ABHR, instructions on ABHR use, a poster on the 'three moments of hand hygiene', and training.** We followed up each mother-baby pair for 3 months after birth and measured rates of consent, recruitment, and follow-up (our target rate was more than 80%). Other measures included ABHR use (the acceptable use was more than four times a day) and its mode of distribution (village health workers (VHWs) or pharmacy), acceptability of study protocol and electronic data capture, and the use of WHO Integrated Management of Childhood Illness (IMCI) tool to screen for newborn infection.

RESULTS:
We selected 36% (10/28) of villages for randomisation to either intervention or control. Over 12 weeks, 176 pregnant women were screened and 58.5% (103/176) were eligible. All, 100% (103/103), eligible women gave consent and were enrolled into the trial (55 intervention and 48 control). After birth, 94.5% (52/55) of mothers in the intervention and 100% (48/48) of mothers in the control villages were followed up within 72 h. Most, 90.9% (50/55), of the mothers in the intervention villages (96.2% of live births) and 95.8% (46/48) of mothers in the control villages (95.9% of live births) were followed up at 3 months**. In intervention villages,**

the average hand rub use was 6.6 times per day. VHWs accounted for all ABHR stock, compared to the pharmacy that could not account for 5 l of ABHR. **The screening tool was positive for infection among a third of babies, i.e. 29.2% (14/48) in the intervention villages versus 31.4% (16/51) in the control villages.**VHWs completed the first four questions of IMCI screening tool with ease and accuracy. There were no adverse reactions with the ABHR.

CONCLUSION:
It is feasible to conduct a cluster-randomised controlled trial (cRCT) of the provision of ABHR to postpartum mothers to prevent neonatal infection-related morbidity in the community in resource-poor settings. Our results indicate that home recruitment promotes excellent follow-up and retention of participants in community trials. The intervention was safe. This pilot study informed the substantial changes necessary in the larger cRCT, including a change in the primary outcome to a composite outcome considering multiple methods of infection detection. A large BabyGel cluster randomised controlled trial is now required.

Pilot Feasibility Stud. 2019 Mar 13;5:43. doi: 10.1186/s40814-019-0428-3. eCollection 2019. (Open access available)

In search of a primary outcome for community-based newborn infection trials in Eastern Uganda: a nested cohort study within the BabyGel pilot trial.

Mobbs NA, Ditai J, Abeso J, Faragher EB, Carrol ED, Gladstone M, Medina-Lara A, Olupot-Olupot P, Weeks AD.
Uganda

BACKGROUND:
Due to their immature immune system, neonates are at high risk of infection. This vulnerability when combined with limited resources and health education in developing countries can lead to sepsis, resulting in high global neonatal mortality rates. Many of these deaths are preventable. The BabyGel pilot trial tested the feasibility of conducting the main randomised trial, with the provision of alcohol handgel to postpartum mothers for prevention of neonatal infective morbidity in the rural community. This secondary analysis sought to evaluate the methods of detecting infections in babies up to 3 months of age.

METHODS:
The pilot two-arm cluster randomised controlled trial took place in 10 villages around Mbale, Eastern Uganda. Women were eligible and recruited antenatally if their gestation was ≥ 34 weeks. All infants of mothers participating in the BabyGel pilot trial were followed up for the first 3 months of life. **Evidence for infant infection was collected using five different methods: clinician diagnosed infection, microbiologically confirmed infection, maternally reported infection, a positive infection screen using the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) screening criteria, and reported antibiotic use identified during home and clinic visits.** These

methods were assessed quantitatively regarding the detection rates of suspected infections and qualitatively by exploring the challenges collecting data in the rural community setting.

RESULTS:
A total of 103 eligible women participated in the BabyGel pilot trial, with 1 woman delivering twins. Of the 99 mother-infant pairs who consented to participate in the study, 55 infants were identified with infection in total. Maternal report of illness provided the highest estimate, with mothers reporting suspected illness for 45 infants (81.8% of the total suspected infections identified). The WHO IMCI screening criteria identified 30 infants with suspected infection (54.5%), and evidence for antibiotic use was established in 22 infants (40%). Finally, clinician-diagnosed infection identified 19 cases (34.5%), which were also microbiologically confirmed in 5 cases (9.1%). Data collection in the rural setting was hindered by poor communication between mothers and the research team, limited staff awareness of the study in health centres resulting in reduced safeguarding of clinical notes, and widespread use of antibiotics prior to notification and clinical review. Furthermore, identification of suspected infection may not have been limited to severe infections, with ambiguity and no official clinical diagnosis being given to those identified solely by maternal report of infection.

CONCLUSIONS:
A high rate of suspected infection was identified spanning the five sources of data collection, but no ideal method was found for detection of community neonatal infection. Although maternal self-reports of infant infection provided the highest detection rate, data collection via each source was limited and may have identified minor rather than major infections. Future studies could utilise the IMCI screening tool to detect severe community infection leading to referral for clinical confirmation. This should be combined with weekly contact with mothers to detect maternally suspected illness. Obtaining more details of the symptoms and timescale will improve the accuracy when detecting the total burden of suspected disease, and advising participants to retain medication packaging and prescriptions will improve identification of antibiotic use.

BMC Public Health. 2019 Jan 3;19(1):1. doi: 10.1186/s12889-018-6343-3. (Open access available)

"We have to clean ourselves to ensure that our children are healthy and beautiful": findings from a qualitative assessment of a hand hygiene poster in rural Uganda.

Harrison BL, Ogara C, Gladstone M, Carrol ED, Dusabe-Richards J, Medina-Lara A, Ditai J, Weeks AD.
Uganda, UK

BACKGROUND:
Neonatal sepsis is a major cause of mortality worldwide, with most deaths occurring in low-income countries. The World Health Organisation (WHO) '5 Moments for Hand Hygiene' poster has been used to reduce hospital-acquired infections, but there is no similar tool to

prevent community-acquired newborn infections in low-resource settings. This assessment, part of the BabyGel Pilot study, evaluated the acceptability of the 'Newborn Moments for Hand Hygiene in the Home' poster. This was an educational tool which aimed to remind mothers in rural Uganda to clean their hands to prevent neonatal infection.

METHODS:
The BabyGel pilot was a cluster randomised trial that assessed the post-partum use of alcohol-based hand rub (ABHR) to prevent neonatal infections in Mbale, Uganda. Fifty-five women in 5 village clusters received the ABHR and used it from birth to 3 months postnatally, with use guided by the new poster. Following the study, 5 focus group discussions (FGDs) were conducted consisting of 6-8 purposively sampled participants from intervention villages. FGDs were audio-recorded, transcribed then translated into English. Transcripts were inductively coded using ATLAS.ti® and qualitatively analysed using thematic content analysis.

RESULTS:
Most mothers reported that they understood the message in the poster ("The picture shows me you must use these drugs to keep your baby healthy") and that they could adhere to the moments from the poster. Some participants used the information from the poster to encourage other caregivers to use the ABHR ("after explaining to them, they liked it"). Other potential moments for hand hygiene were introduced by participants, such as after tending to domestic animals and gardening.
CONCLUSION:
The poster was well-received, and participants reported compliance with the moments for hand hygiene (although the full body wipe of the baby has since been removed). The poster will be adapted into a sticker format on the ABHR bottle. More focus could be put into an education tool for other caregivers who wish to hold the baby. Overall, the study demonstrated the acceptability of an adapted version of the WHO Moments for Hand Hygiene poster in the introduction of an intervention in the community.

Health worker education

J Contin Educ Health Prof. 2018 Summer;38(3):205-212. doi: 10.1097/CEH.0000000000000211.

Health Care Simulation in Developing Countries and Low-Resource Situations.

Martinerie L, Rasoaherinomenjanahary F, Ronot M, Fournier P, Dousset B, Tesnière A, Mariette C, Gaujoux S, Gronnier C.
Switzerland, France

INTRODUCTION:
Health care simulation, as a complement to traditional learning, has spread widely and seems to benefit both students and patients. The teaching methods involved in health care simulation require substantial human, logistical, and financial investments that might preclude their spread in developing countries. The aim of this study was to analyze the health care simulation experiences in developing countries.

METHODS:
A comprehensive literature search was performed from January 2000 to December 2016. Articles reporting studies on educational health care simulation in developing countries were included.

RESULTS:
In total, 1161 publications were retrieved, of which 156 were considered eligible based on title and abstract screening. Thirty articles satisfied our predefined selection criteria. Most of the studies were case series; 76.7% (23/30) were prospective and comparative, and five were randomized trials. The development of dedicated task trainers and telesimulation were the primary techniques assessed. The retrieved studies showed encouraging trends in terms of trainee satisfaction with improvement after training, but the improvements were mainly tested on the training tool itself. Two of the tools have been proven to be construct valid with clinical impact.

CONCLUSION:
Health care simulation in developing countries seems feasible with encouraging results. Higher-quality studies are required to assess the educational value and promote the development of health care simulation programs.

Haematological disorders

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

BMC Infect Dis. 2018 Dec 12;18(1):650. doi: 10.1186/s12879-018-3556-0. (Open access available)

Safety and effectiveness of antimalarial therapy in sickle cell disease: a systematic review and network meta-analysis.

Frimpong A, Thiam LG, Arko-Boham B, Owusu EDA, Adjei GO.
Ghana, Switzerland

BACKGROUND:
About 80% of all reported sickle cell disease (SCD) cases in children anually are recorded in Africa. Although malaria is considered a major cause of death in SCD children, there is limited data on the safety and effectiveness of the available antimalarial drugs used for prophylaxis. Also, previous systematic reviews have not provided quantitative measures of preventive effectiveness. The purpose of this research was to conduct a systematic review and meta-

analysis of the available literature to determine the safety and effectiveness of antimalarial chemoprophylaxis used in SCD patients.

METHODS:
We searched in PubMed, Medline, CINAHL, POPLine and Cochrane library, for the period spanning January 1990 to April 2018. We considered randomized or quasi-randomized controlled trials comparing any antimalarial chemoprophylaxis to, 1) other antimalarial chemoprophylaxis, 2) placebo or 3) no intervention, in SCD patients. Studies comparing at least two treatment arms, for a minimum duration of three months, with no restriction on the number of patients per arm were reviewed. The data were extracted and expressed as odds ratios. Direct pairwise comparisons were performed using fixed effect models and the heterogeneity assessed using the I-square.

RESULTS:
Six qualified studies that highlighted the importance of antimalarial chemoprophylaxis in SCD children were identified. In total, seven different interventions (Chloroquine, Mefloquine, Mefloquine artesunate, Proguanil, Pyrimethamine, Sulfadoxine-pyrimethamine, Sulfadoxine-pyrimethamine amodiaquine) were evaluated in 912 children with SCD. **Overall, the meta-analysis showed that antimalarial chemoprophylaxis provided protection against parasitemia and clinical malaria episodes in children with SCD. Nevertheless, the risk of hospitalization (OR = 0.72, 95% CI = 0.267-1.959; I = 0.0%), blood transfusion (OR = 0.83, 95% CI = 0.542-1.280; I = 29.733%), vaso-occlusive crisis (OR = 19, 95% CI = 1.713-2.792; I = 93.637%), and mortality (OR = 0.511, 95% CI = 0.189-1.384; I = 0.0%) did not differ between the intervention and placebo groups**.

CONCLUSION:
The data shows that antimalarial prophylaxis reduces the incidence of clinical malaria in children with SCD. However, there was no difference between the occurrence of adverse events in children who received placebo and those who received prophylaxis. This creates an urgent need to assess the efficacy of new antimalarial drug regimens as potential prophylactic agents in SCD patients.

Heart disease

Rheumatic heart disease

Indian Heart J. 2018 Dec;70 Suppl 3:S74-S81. doi: 10.1016/j.ihj.2018.05.015. Epub 2018 May 30. (Open access available)

School-based surveillance for detection of children with acute pharyngitis, rheumatic fever/rheumatic heart disease in Shimla district, Himachal Pradesh, India-A cluster randomized controlled trial.

Negi PC, Merwaha R, Rao S, Asotra S, Mahajan A, Joshi A.
India, USA

BACKGROUND:
The lack of surveillance system is a major barrier in prevention and control of rheumatic fever/rheumatic heart disease (RF/RHD). Efficacy of school-based surveillance was evaluated for detection of acute pharyngitis and RF/RHD in Shimla district, HP.

METHODS:
The schools in district Shimla were randomly assigned to intervention and controlled arm (442 vs. 441 schools). The trained nodal teachers reported children with symptoms of acute pharyngitis and or RF/RHD in intervention arm and children taken to hospitals by parents for symptoms of acute pharyngitis and or RF/RHD under control arm through mobile phone to coordinating centre. Final outcome for presence of RF/RHD or other heart Diseases was recorded after examination at nearest primary health centers and/or at Indira Gandhi Medical College Hospital, Shimla. Difference in detection rate between intervention arm and control arm was compared using Z test.

RESULTS:
The number of school children reported from intervention group was significantly higher than in control due to suspected symptoms of acute pharyngitis and or RF/RHD were 65 (2.84/1000) and 15 (0.60/1000), respectively ($p < 0.01$). Only 4 children in each arm were found to have heart diseases, with prevalence of (0.17/1000 and 0.16/1000), respectively, after clinical and echocardiography evaluation. In intervention arm, one child had RHD while three had congenital heart disease; in control arm, one child had congenital heart disease and three had RHD.

CONCLUSIONS:
School based surveillance had higher rate of suspecting children with acute pharyngitis and or RF/RHD although with low specificity. There is a need of future studies to demonstrate the effectiveness of the proposed intervention in endemic regions of the state.

Heart. 2018 Sep 12. pii: heartjnl-2018-313614. doi: 10.1136/heartjnl-2018-313614. (Open access available)

Digoxin and clinical outcomes in the Global Rheumatic Heart Disease Registry.

Karthikeyan G, Devasenapathy N, Zühlke L, Engel ME, Rangarajan S, Teo KK, Mayosi BM, Yusuf S; Global Rheumatic Heart Disease Registry (REMEDY) Investigators.
India, South Africa, Canada

OBJECTIVE:
Digoxin is widely used in patients with rheumatic heart disease (RHD) despite a lack of data on its impact on clinical outcomes. We aimed to determine the association of digoxin use on clinical outcomes in patients with RHD.

METHODS:
We performed a retrospective analysis of the association of digoxin use with mortality at 2 years in a large RHD registry. Secondary outcomes were recurrent heart failure (HF) and hospitalisation for any cause. We assessed associations using multivariable logistic regression in the entire cohort and in subgroups of patients with atrial fibrillation (AF) and HF. We also estimated average treatment effects from propensity-adjusted analyses using inverse probability treatment weighting.

RESULTS:
Information on digoxin use at baseline was available for 98.7% (3298/3343) of patients. In the overall population, **digoxin was significantly associated with mortality (OR 1.63, 95% CI 1.30 to 2.04, p<0.0001)** and recurrent HF (OR 1.48, 95% CI 1.07 to 2.04, p=0.019). On propensity-weighted analyses, this effect was markedly attenuated (OR 1.05, 95% CI 1.01 to 1.09, p=0.005). **Patients in sinus rhythm without HF had a higher propensity-adjusted odds of death with digoxin use (OR 1.06, 95% CI 1.01 to 1.12, p=0.015), but those with both AF and HF had lower mortality (OR 0.88, 95% CI 0.80 to 0.98, p=0.019).**

CONCLUSION:
Digoxin use is associated with higher mortality in patients with RHD, but this is greatly attenuated on propensity adjustment, indicating the presence of substantial treatment bias. The adjusted estimates may therefore not be reliable, and large randomised trials are needed to determine the true effect of digoxin in patients with RHD.

Comment
Although this is not an RCT, it suggests that digoxin is beneficial for rheumatic heart disease patients with AF and heart failure, and not useful without either of these complications of ARF/RHD.

Congenital heart disease and cardiac surgery

PLoS One. 2019 May 9;14(5):e0213862. doi: 10.1371/journal.pone.0213862. eCollection 2019. (Open access available)

N-acetylcysteine use among patients undergoing cardiac surgery: A systematic review and meta-analysis of randomized trials.

Pereira JEG, El Dib R, Braz LG, Escudero J, Hayes J, Johnston BC.

BACKGROUND:
Cardiac surgeries are complex procedures aiming to re-establish coronary flow and correct valvular defects. Oxidative stress, caused by inflammation and ischemia-reperfusion injury, is associated with these procedures, increasing the risk of adverse outcomes. N-acetylcysteine (NAC) acts as an antioxidant by replenishing the glutathione stores, and emerging evidence suggests that NAC may reduce the risk of adverse perioperative outcomes. We conducted a systematic review and meta-analysis to investigate the addition of NAC to a standard of care among adult patients undergoing cardiac surgery.

METHODS:
We searched four databases (PubMed, EMBASE, CENTRAL, LILACS) from inception to October 2018 and the grey literaure for randomized controlled trials (RCTs) investigating the effect of NAC on pre-defined outcomes including mortality, acute renal insufficiency (ARI), acute cardiac insufficiency (ACI), hospital length of stay (HLoS), intensive care unit length of stay (ICULoS), arrhythmia and acute myocardial infarction (AMI). Reviewers independently screened potentially eligible articles, extracted data and assessed the risk of bias among eligible articles. We used the GRADE approach to rate the overall certainty of evidence for each outcome.

RESULTS:
Twenty-nine RCTs including 2,486 participants proved eligible. Low to moderate certainty evidence demonstrated that the addition of NAC resulted in a non-statistically significant reduction in mortality (Risk Ratio (RR) 0.71; 95% Confidence Interval (CI) 0.40 to 1.25), ARI (RR 0.92; 95% CI 0.79 to 1.09), ACI (RR 0.77; 95% CI 0.44 to 1.38), HLoS (Mean Difference (MD) 0.21; 95% CI -0.64 to 0.23), ICULoS (MD -0.04; 95% CI -0.29 to 0.20), arrhythmia (RR 0.79; 95% CI 0.52 to 1.20), and AMI (RR 0.84; 95% CI 0.48 to 1.48).

LIMITATIONS:
Among eligible trials, we observed heterogeneity in the population and interventions including patients with and without kidney dysfunction and interventions that differed in route of administration, dosage, and duration of treatment. This observed heterogeneity was not explained by our subgroup analyses.

CONCLUSIONS:
The addition of NAC during cardiac surgery did not result in a statistically significant reduction in clinical outcomes. A large randomized placebo-controlled multi-centre trial is needed to determine whether NAC reduces mortality.

J Ayub Med Coll Abbottabad. 2018 Jul-Sep;30(3):333-336. (Open access available)

Comparison Of The Efficacy Of Sildenafil Alone Versus Sildenafil Plus Bosentan In Newborns With Persistent Pulmonary Hypertension.

Fatima N, Arshad S, Quddusi AI, Rehman A, Nadeem A, Iqbal I.
Pakistan

BACKGROUND:
Persistent pulmonary hypertension is a serious disease among new-borns. Inhaled nitric oxide is first line of therapy along with extracorporeal membrane oxygenation. Pulmonary vasodilators such as sildenafil, bosentan and milrinone are also used to treat persistent pulmonary hypertension especially in resource limited centres where inhaled nitric oxide is not available. The objective of this study was **to compare the effect of sildenafil alone and sildenafil with bosentan on severity of tricuspid regurgitation and duration of hospitalization in new-borns with persistent pulmonary hypertension**.

METHODS:
This was single blinded clinical trial conducted at The Children's Hospital & the Institute of Child Health, Multan, Pakistan, from July 2016 to December 2016. New-borns with pulmonary hypertension were admitted and divided into two groups. **Group A was treated with sildenafil (2mg per kg per dose three times a day) and group B with both sildenafil (2 mg per kg per dose three times a day) and bosentan (1 mg per kg per dose twice a day).**

RESULTS:
There were 50 new-borns in each group. The mean age, sex distribution and baseline TR measurement (mmHg) at the time of admission was similar in both the groups. **Measurement of TR (mmHg) after 72 hours admission was significantly less in Group B as compared to group A (11±4.62 versus 23±4.78), p-value<0.0001. The mean duration of hospital stays (days) was 10.12±5.20 in group A and 7.56±3.77 in group B (p-value <0.0001). There was no mortality in any group and no case of hypotension in both groups.**

CONCLUSIONS:
The combined use of sildenafil and bosentan is more effective than sildenafil alone for control of pulmonary hypertension in resource limited centres.

Comment
The fact that mortality was zero in both groups suggests that the study population was a low-risk group.

Asian Cardiovasc Thorac Ann. 2019 Feb;27(2):75-79. doi: 10.1177/0218492318820992. Epub 2018 Dec 22. (Open access available)

Comparison between blood and non-blood cardioplegia in tetralogy of Fallot.

Romolo H, Hernisa L, Fakhri D, Rachmat J, Dwi Mulia D, Rahmat B.
Indonesia

Abstract
BACKGROUND:
Cardioplegia is an integral part of myocardial protection. The superiority of blood cardioplegia in adult patients has been reported. However, this is yet to be studied in cyanotic pediatric patients.

METHODS:
A randomized open-label trial was conducted in 70 patients with tetralogy of Fallot. They were divided into two groups: 35 patients had crystalloid cardioplegia (controls), and 35 had blood cardioplegia. Lactate and coronary oxygen extraction in arterial blood and the coronary sinus were measured immediately after cessation of cardiopulmonary bypass, 15 and 30 min later. Postoperative mortality, major adverse cardiac events, mechanical

ventilation time, inotrope administration, arrhythmias, right ventricular function, intensive care unit and hospital length of stay were observed.

RESULTS:
There were no significant differences in clinical outcomes or lactate levels. There was a significant difference in coronary oxygen extraction immediately and 15 min after cessation of cardiopulmonary bypass (p = 0.038, p = 0.015).

CONCLUSION:
Blood cardioplegia gave a better postoperative oxygen extraction value but there were no differences in myocardial damage or clinical outcome between the two groups.

J Cardiothorac Vasc Anesth. 2018 Dec;32(6):2633-2640. doi: 10.1053/j.jvca.2018.04.028. Epub 2018 Apr 12.

Randomized Controlled Trial of Heparin Versus Bivalirudin Anticoagulation in Acyanotic Children Undergoing Open Heart Surgery.

Hasija S, Talwar S, Makhija N, Chauhan S, Malhotra P, Chowdhury UK, Krishna NS, Sharma G.
India

OBJECTIVE:
To determine the safety and efficacy of bivalirudin as an anticoagulant for pediatric open heart surgery (OHS) and to determine its appropriate dosage for this purpose.

DESIGN:
Prospective, randomized controlled trial.

SETTING:
Tertiary care hospital.

PARTICIPANTS:
Fifty acyanotic children aged 1-12 years undergoing OHS.

INTERVENTIONS:
The children were randomized to receive either 4 mg/kg of heparin (n = 25, group H) or 1 mg/kg of bivalirudin bolus followed by 2.5 mg/kg/h infusion (n = 25, group B) as the anticoagulant. The doses were adjusted to maintain activated clotting time (ACT) above 480 seconds. At the conclusion of surgery, protamine (1.3 mg/100 U of heparin) was administered to children in group H.

MEASUREMENTS AND MAIN RESULTS:
The children were comparable in both groups with regard to demographic characteristics. The mean age and weight were 51.5 months and 13.4 kg in group H, and 59.3 months and 13.4 kg in group B. The dose of anticoagulant required was 4.0 ± 0.2 mg/kg in group H and 1.7 ± 0.2 mg/kg followed by 3.0 ± 0.7 mg/kg/h infusion in group B (p < 0.001). One child in group

H required an additional dose compared to 13 (54.2%) children in group B. Intraoperatively, the ACT achieved was higher in group H compared to group B ($p < 0.05$). The ACT returned to baseline value after protamine administration in group H, but it remained elevated for 2 hours after termination of cardiopulmonary bypass (CPB) in group B ($p < 0.01$). The ACT was higher in group B compared to group H for 6 hours after termination of CPB ($p < 0.05$). Heparin prolonged the onset of clotting, decreased the rate and strength of thrombus formation, and inhibited platelet function to a greater extent than bivalirudin on viscoelastic coagulation testing. The total duration of surgery was prolonged in group B. The postoperative chest tube drainage was similar in group B (4.9 mL/kg) as in group H (5.9 mL/kg) in spite of higher ACT. The transfusion requirements were similar. No adverse event occurred in any patient.

CONCLUSION:
Bivalirudin is a safe and effective anticoagulant for pediatric OHS. Though it is not suitable as a routine anticoagulant for this purpose, it may be used as a heparin alternative in instances when heparin cannot be used. The dose required to maintain ACT for more than 480 seconds was 1.7 ± 0.2 mg/kg followed by 3.0 ± 0.7 mg/kg/h infusion. The ACT remained elevated for 2 hours after stopping the infusion. Bivalirudin did not increase postoperative bleeding and transfusion requirement.

J Cardiothorac Vasc Anesth. 2019 Feb;33(2):418-425. doi: 10.1053/j.jvca.2018.08.209. Epub 2018 Aug 31.

Comparison of the Efficacy of Ultrasound-Guided Serratus Anterior Plane Block, Pectoral Nerves II Block, and Intercostal Nerve Block for the Management of Postoperative Thoracotomy Pain After Pediatric Cardiac Surgery.

Kaushal B, Chauhan S, Saini K, Bhoi D, Bisoi AK, Sangdup T, Khan MA.
India

OBJECTIVE:
The aim of this study was to compare the relative efficacy of ultrasound-guided serratus anterior plane block (SAPB), pectoral nerves (Pecs) II block, and intercostal nerve block (ICNB) for the management of post-thoracotomy pain in pediatric cardiac surgery.

DESIGN:
A prospective, randomized, single-blind, comparative study.

SETTING:
Single-institution tertiary referral cardiac center.

PARTICIPANTS:
The study comprised 108 children with congenital heart disease requiring surgery through a thoracotomy.

INTERVENTIONS:
Children were allocated randomly to 1 of the 3 groups: SAPB, Pecs II, or ICNB. All participants received 3 mg/kg of 0.2% ropivacaine for ultrasound-guided block after induction of anesthesia. Postoperatively, intravenous paracetamol was used for multimodal and fentanyl was used for rescue analgesia.

MEASUREMENTS AND MAIN RESULTS:
A modified objective pain score (MOPS) was evaluated at 1, 2, 4, 6, 8, 10, and 12 hours post-extubation. The early mean MOPS at 1, 2, and 4 hours was similar in the 3 groups. The late mean MOPS was significantly lower in the SAPB group compared with that of the ICNB group ($p < 0.001$). The Pecs II group also had a lower MOPS compared with the ICNB group at 6, 8, and 10 hours ($p < 0.001$), but the MOPS was comparable at hour 12 ($p = 0.301$). The requirement for rescue fentanyl was significantly higher in ICNB group in contrast to the SAPB and Pecs II groups.

CONCLUSION:
SAPB and Pecs II fascial plane blocks are equally efficacious in post-thoracotomy pain management compared with ICNB, but they have the additional benefit of being longer lasting and are as easily performed as the traditional ICNB.

HIV / AIDS

Antiretroviral therapy (ART)

PLoS Med. 2018 Dec 4;15(12):e1002706. doi: 10.1371/journal.pmed.1002706. eCollection 2018 Dec. (Open access available)

Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial.

Kityo C, Szubert AJ, Siika A, Heyderman R, Bwakura-Dangarembizi M, Lugemwa A, Mwaringa S, Griffiths A, Nkanya I, Kabahenda S, Wachira S, Musoro G, Rajapakse C, Etyang T, Abach J, Spyer MJ, Wavamunno P, Nyondo-Mipando L, Chidziva E, Nathoo K, Klein N, Hakim J, Gibb DM, Walker AS, Pett SL; REALITY trial team.
Uganda, UK, Malawi, Zimbabwe, Kenya, Australia

BACKGROUND:
In sub-Saharan Africa, individuals infected with HIV who are severely immunocompromised have high mortality (about 10%) shortly after starting antiretroviral therapy (ART). This group also has the greatest risk of morbidity and mortality associated with immune reconstitution inflammatory syndrome (IRIS), a paradoxical response to successful ART. Integrase inhibitors lead to significantly more rapid declines in HIV viral load (VL) than all other ART classes. We hypothesised that intensifying standard triple-drug ART with the integrase inhibitor,

raltegravir, would reduce HIV VL faster and hence reduce early mortality, although this strategy could also risk more IRIS events.

METHODS AND FINDINGS:
In a 2×2×2 factorial open-label parallel-group trial, treatment-naive adults, adolescents, and children >5 years old infected with HIV, with cluster of differentiation 4 (CD4) <100 cells/mm3, from eight urban/peri-urban HIV clinics at regional hospitals in Kenya, Malawi, Uganda, and Zimbabwe were randomised 1:1 to initiate standard triple-drug ART, with or without 12-week raltegravir intensification, and followed for 48 weeks. The primary outcome was 24-week mortality, analysed by intention to treat. Of 2,356 individuals screened for eligibility, 1,805 were randomised between 18 June 2013 and 10 April 2015. Of the 1,805 participants, 961 (53.2%) were male, 72 (4.0%) were children/adolescents, median age was 36 years, CD4 count was 37 cells/mm3, and plasma viraemia was 249,770 copies/mL. Fifty-six participants (3.1%) were lost to follow-up at 48 weeks. By 24 weeks, 97/902 (10.9%) raltegravir-intensified ART versus 91/903 (10.2%) standard ART participants had died (adjusted hazard ratio [aHR] = 1.10 [95% CI 0.82-1.46], p = 0.53), with no evidence of interaction with other randomisations (pheterogeneity > 0.7) and despite significantly greater VL suppression with raltegravir-intensified ART at 4 weeks (343/836 [41.0%] versus 113/841 [13.4%] with standard ART, p < 0.001) and 12 weeks (567/789 [71.9%] versus 415/803 [51.7%] with standard ART, p < 0.001). Through 48 weeks, there was no evidence of differences in mortality (aHR = 0.98 [95% CI 0.76-1.28], p = 0.91); in serious (aHR = 0.99 [0.81-1.21], p = 0.88), grade-4 (aHR = 0.88 [0.71-1.09], p = 0.29), or ART-modifying (aHR = 0.90 [0.63-1.27], p = 0.54) adverse events (the latter occurring in 59 [6.5%] participants with raltegravir-intensified ART versus 66 [7.3%] with standard ART); in events judged compatible with IRIS (occurring in 89 [9.9%] participants with raltegravir-intensified ART versus 86 [9.5%] with standard ART, p = 0.79) or in hospitalisations (aHR = 0.94 [95% CI 0.76-1.17], p = 0.59). At 12 weeks, one and two raltegravir-intensified participants had predicted intermediate-level and high-level raltegravir resistance, respectively. At 48 weeks, the nucleoside reverse transcriptase inhibitor (NRTI) mutation K219E/Q (p = 0.004) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations K101E/P (p = 0.03) and P225H (p = 0.007) were less common in virus from participants with raltegravir-intensified ART, with weak evidence of less intermediate- or high-level resistance to tenofovir (p = 0.06), abacavir (p = 0.08), and rilpivirine (p = 0.07). Limitations of the study include limited clinical, radiological, and/or microbiological information for some participants, reflecting available services at the centres, and lack of baseline genotypes.

CONCLUSIONS:
Although 12 weeks of raltegravir intensification was well tolerated and reduced HIV viraemia significantly faster than standard triple-drug ART during the time of greatest risk for early death, this strategy did not reduce mortality or clinical events in this group and is not warranted. There was no excess of IRIS-compatible events, suggesting that integrase inhibitors can be used safely as part of standard triple-drug first-line therapy in severely immunocompromised individuals.

Early infant diagnosis

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

Lancet HIV. 2018 Dec;5(12):e696-e705. doi: 10.1016/S2352-3018(18)30245-5. Epub 2018 Oct 8.

Evaluation of the HIV Infant Tracking System (HITSystem) to optimise quality and efficiency of early infant diagnosis: a cluster-randomised trial in Kenya.

Finocchario-Kessler S, Gautney B, Cheng A, Wexler C, Maloba M, Nazir N, Khamadi S, Lwembe R, Brown M, Odeny TA, Dariotis JK, Sandbulte M, Mabachi N, Goggin K.
USA, Kenya

BACKGROUND:
The HIV Infant Tracking System (HITSystem) is a web-based intervention linking providers of early infant diagnosis, laboratory technicians, and mothers and infants to improve outcomes for HIV-exposed infants. We aimed to evaluate the efficacy of the HITSystem on key outcomes of early infant diagnosis.

METHODS:
We did a cluster-randomised trial at six hospitals in Kenya, which were matched on geographic region, resource level, and volume of patients (high, medium, and low). **We randomly allocated hospitals within a matched pair to either the HITSystem (intervention; n=3) or standard of care (control; n=3).** A random number generator was used to assign clusters. Investigators were unaware of the randomisation process. **Eligible participants were mothers aged 18 years or older with an infant younger than 24 weeks presenting for their first early infant diagnosis appointment. The primary outcome was complete early infant diagnosis retention, which was defined as receipt of all indicated age-specific interventions until 18 months post partum (for HIV-negative infants) or antiretroviral therapy initiation (for HIV-positive infants).** Analysis was per protocol in all randomised pairs judged eligible, excluding infant deaths and those who moved or were transferred to another health facility. Modified intention-to-treat sensitivity analyses judged all infant deaths and transfers as incomplete early infant diagnosis retention. Separate multivariable logistic regression analyses were done with intervention group, hospital volume, and significant covariates as fixed effects.

FINDINGS:
Between Feb 16, 2014, and Dec 31, 2015, 895 mother-infant pairs were enrolled. Of these, 87 were judged ineligible for analysis, 26 infants died, and 92 pairs moved or were transferred to another health facility. Thus, **data from 690 mother-infant pairs were analysed, of whom 392 were allocated to the HITSystem and 298 to standard of care.** Mother-infant pairs were followed up to Sept 30, 2017. Infants diagnosed as HIV-positive were followed up for a median of 2·1 months (IQR 1·6-4·8) and HIV-negative infants were followed up for a median of 17·0 months (IQR 16·6-17·6). **Infants enrolled in the HITSystem were significantly more likely to receive complete early infant diagnosis services compared with those assigned standard of care (334 of 392 [85%] vs 180 of 298 [60%]; adjusted odds ratio [OR] 3·7, 95% CI 2·5-5·5; p<0·0001).** No intervention effect was recorded at high-volume hospitals, but strong effects were seen at medium-volume and low-volume hospitals. Modified

intention-to-treat analyses for complete early infant diagnosis were also significant (334 of 474 [70%] vs 180 of 334 [54%]; adjusted OR 2·0, 95% CI 1·4-2·7; p<0·0001). No adverse events related to study participation were reported.

INTERPRETATION:
The HITSystem intervention is effective and feasible to implement in low-resource settings. The HITSystem algorithms have been modified to include HIV testing at birth, and an adapted HITSystem 2.0 version is supporting HIV-positive pregnant women to prevent perinatal transmission and optimise maternal and infant outcomes.

Cotrimoxazole preventative therapy

PLoS Negl Trop Dis. 2019 Mar 21;13(3):e0007223. doi: 10.1371/journal.pntd.0007223. eCollection 2019 Mar. (Open access available)

The prevalence and antifolate drug resistance profiles of Plasmodium falciparum in study participants randomized to discontinue or continue cotrimoxazole prophylaxis.

Juma DW, Muiruri P, Yuhas K, John-Stewart G, Ottichilo R, Waitumbi J, Singa B, Polyak C, Kamau E.

OBJECTIVE:
Cotrimoxazole prevents opportunistic infections including falciparum malaria in HIV-infected individuals but there are concerns of cross-resistance to other antifolate drugs such as sulphadoxine-pyrimethamine (SP). In this study, we investigated the prevalence of antifolate-resistance mutations in Plasmodium falciparum that are associated with SP resistance in HIV-infected individuals on antiretroviral treatment randomized to discontinue (STOP-CTX), or continue (CTX) cotrimoxazole in Western Kenya.

DESIGN:
Samples were obtained from an unblinded, non-inferiority randomized controlled trial where participants were recruited on a rolling basis for the first six months of the study, then followed-up for 12 months with samples collected at enrollment, quarterly, and during sick visits.

METHOD:
Plasmodium DNA was extracted from blood specimens. Initial screening to determine the presence of Plasmodium spp. was performed by quantitative reverse transcriptase real-time PCR, followed by genotyping for the presence of SP-resistance associated mutations by Sanger sequencing.

RESULTS:
The prevalence of mutant haplotypes associated with SP-resistant parasites in pfdhfr (51I/59R/108N) and pfdhps (437G/540E) genes were significantly higher (P = 0.0006 and P = 0.027, respectively) in STOP-CTX compared to CTX arm. The prevalence of quintuple

haplotype (51I/59R/108N/437G/540E) was 51.8% in STOP-CTX vs. 6.3% (P = 0.0007) in CTX arm. There was a steady increase in mutant haplotypes in both genes in STOP-CTX arm overtime through the study period, reaching statistical significance (P < 0.0001).

CONCLUSION:
The frequencies of mutations in pfdhfr and pfdhps genes were higher in STOP-CTX arm compared to CTX arm, suggesting cotrimoxazole effectively controls and selects against SP-resistant parasites.

Management of HIV-related conditions

Pan Afr Med J. 2018 Apr 9;29:208. doi: 10.11604/pamj.2018.29.208.15240. eCollection 2018. (Open access available)

Treatment interventions for diarrhoea in HIV-infected and HIV-exposed children: a systematic review.

Motaze NV, Nwachukwu C, Humphreys E.
Cameroon, South Africa, Nigeria, USA

Introduction:
Seventy percent of an estimated 10 million children less than five years of age in developing countries die each year of acute respiratory infections, diarrhoea, measles, malaria, malnutrition or a combination of these conditions. Children living with Human immunodeficiency virus (HIV) are at risk of diarrhoea because of drug interactions with antiretroviral therapy and bottle feeding. This may be aggravated by malnutrition and other infectious diseases which are frequent in children living with HIV. Objective: **to evaluate treatment interventions for diarrhoea in HIV infected and exposed children.**

Methods:
A comprehensive search was conducted on 02 June 2016 to identify relevant studies for inclusion. We included randomised controlled trials of HIV infected or exposed children under 15 years of age with diarrhoea. Two authors independently selected studies for inclusion, assessed risk of bias (RoB) and extracted data using a pre-designed data extraction form.

Results:
We included two studies (Amadi 2002 and Mda 2010) that each enrolled 50 participants. The RoB was assessed as low-risk for both included studies. **There was no difference in clinical cure and all-cause mortality between nitazoxanide and placebo for cryptosporidial diarrhoea in Amadi 2002.** In Mda 2010, there was a reduction in duration of hospitalisation in the micronutrient supplement group (P < 0.005) although there was no difference in all-cause mortality.

Conclusion:

There is low certainty evidence on the effectiveness of nitazoxanide for treating cryptosporidial diarrhoea and micronutrient supplementation in children with diarrhoea. Adequately powered trials are needed to assess micronutrients and nitazoxanide, as well as other interventions, for diarrhoea in HIV-infected and-exposed children.

Vaccines in HIV-infected children

Hum Vaccin Immunother. 2019 Apr 4. doi: 10.1080/21645515.2019.1599677. (Open access available)

Vaccination among HIV-infected, HIV-exposed uninfected and HIV-uninfected children: A systematic review and meta-analysis of evidence related to vaccine efficacy and effectiveness.

Adetokunboh OO, Ndwandwe D, Awotiwon A, Uthman OA, Wiysonge CS.

Evidence-based approaches were used in making recommendations for vaccination against vaccine-preventable diseases for HIV-infected and HIV-exposed individuals but with limited substantiation. We conducted a systematic review and meta-analysis with randomised-controlled trials (RCTs), cohort and case-control studies that have efficacy and effectiveness of vaccines in HIV-infected and HIV-exposed children as outcomes. Web of Science, Cochrane Library, PubMed and Scopus databases were searched for articles. Efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) against total vaccine serotype invasive pneumococcal disease was 32% in HIV-infected children and 78% among HIV-uninfected children. Vaccine effectiveness of Bacillus Calmette-Guérin vaccine in preventing tuberculosis in HIV-infected children was zero compared to 59% protection in HIV-unexposed children. Likewise, HIV-uninfected children have better protection against invasive Haemophilis influenzae type b disease than the HIV-infected children. Effectiveness studies of rotavirus vaccines show that HIV-exposed uninfected children have similar protection against rotavirus gastroenteritis compared to the non-exposed children. Children who are severely immunosuppressed are poorly protected against invasive pneumococcal diseases. HIV-infected children tend to have lesser vaccine protection against vaccine-preventable diseases when compared to unexposed children. HIV-infected children who are immunocompetent are more likely to have better vaccine protection against vaccine-preventable diseases than those who are immunosuppressed. The overall quality of the observational studies was very low with very little confidence in the effect estimate. The overall quality of evidence for the RCT outcomes was mainly high. This study reveals a dearth of efficacy and effectiveness studies among HIV-infected and exposed children.

Nutrition, growth and development of children with HIV

BMC Pregnancy Childbirth. 2018 Dec 17;18(1):500. doi: 10.1186/s12884-018-2136-z. (Open access available)

Mid-arm muscle area and anthropometry predict low birth weight and poor pregnancy outcomes in Tanzanian women with HIV.

Petraro P, Madzorera I, Duggan CP, Spiegelman D, Manji K, Kisenge R, Kupka R, Fawzi WW.
USA, Tanzania

BACKGROUND:
An observational study was conducted to examine the role of maternal anthropometry, including mid-arm muscle area (MAMA) and others, as risk factors for low birth weight (LBW), small for gestational age (SGA) and preterm births in human immunodeficiency virus (HIV) infected pregnant women. HIV-positive women (N = 2369), between 12 and 32 weeks gestation were followed through delivery in Tanzania, from 2003 to 2008. Participants were women enrolled in a randomized, double-blind, placebo-controlled, clinical trial who delivered live births.

METHODS:
Binomial regression analysis was used to evaluate the association of maternal nutritional indicators of MAMA, mid-upper arm circumference (MUAC), body mass index (BMI) and maternal weight with LBW, SGA and preterm in multivariate analysis.

RESULTS:
Higher MAMA was associated with a 32% lower risk of LBW compared to lower measurements (RR = 0.68, 95% CI = 0.50-0.94). Similar protective associations were noted for higher BMI (RR = 0.58, 95% CI = 0.42-0.79); maternal weight (RR = 0.50, 95% CI = 0.36-0.69) and MUAC (RR = 0.62, 95% CI = 0.45-0.86). Higher MAMA was also associated with lower risk of SGA (RR = 0.78, 95% CI = 0.68-0.90) and marginally associated with preterm (RR = 0.85, 95% CI = 0.69-1.04). Beneficial associations of MUAC, BMI and maternal weight with SGA and preterm were also observed.

CONCLUSION:
MAMA performs comparably to MUAC, maternal weight and BMI, as a predictor of LBW and SGA in HIV-infected women. The possible role of MAMA and other indicators in screening HIV positive women at risk of adverse pregnancy outcomes should be investigated.

Medicine (Baltimore). 2018 Nov;97(47):e12910. doi: 10.1097/MD.0000000000012910. (Open access available)

Efficacy of rational emotive digital storytelling intervention on knowledge and risk perception of HIV/AIDS among schoolchildren in Nigeria.

Ezegbe B, Eseadi C, Ede MO, Igbo JN, Aneke A, Mezieobi D, Ugwu GC, Ugwoezuonu AU, Elizabeth E, Ede KR, Ede AO, Ifelunni CO, Amoke C, Eneogu ND, Effanga OA.
Nigeria

BACKGROUND:
This investigation was aimed at determining the efficacy of a rational emotive digital storytelling (REDStory) therapy on knowledge and perception of risk of HIV/AIDS among schoolchildren in Enugu State, Nigeria.

METHODS:
The researchers adopted a group randomized controlled trial design involving a pretest, posttest, and follow-up design involving a treatment group and a waiting-list control group. Participants were 80 junior secondary schoolchildren attending public and private schools who met the criteria for inclusion in the sample of this study. The REDStory intervention program lasted for 8-week duration of REDStory therapy. The HIV Knowledge Questionnaire and the Perceived Risk of HIV Scale (PRHS) were used for data collection for this study. Repeated measures analysis of variance and t test were used for data analysis.

RESULTS:
The results revealed that REDStory therapy had a significant effect in increasing knowledge level and perceived risk of HIV among schoolchildren compared to those in waitlisted control group. Lastly, the positive benefits of this study were significantly sustained by the treatment group at the follow-up.

CONCLUSION:
The current study therefore suggests the use of REDStory therapy in increasing knowledge and perception of risk of HIV/AIDS among schoolchildren in Enugu, Nigeria.
PMID:

p Ther Int. 2018 Dec 19;2018:3652529. doi: 10.1155/2018/3652529. eCollection 2018. (Open access available)

A Feasibility RCT Evaluating a Play-Informed, Caregiver-Implemented, Home-Based Intervention to Improve the Play of Children Who Are HIV Positive.

Ramugondo E, Ferreira A, Chung D, Cordier R.
South Africa, Australia

Background/aim:
In South Africa, contextual factors have been identified as barriers to outdoor, unstructured play. The human immunodeficiency virus (HIV) and resulting progressive HIV encephalopathy (PHE) is a pandemic in this area, associated with development delays that are not addressed by highly active antiretroviral treatment (HAART). This study aimed to describe the playfulness in children with HIV and PHE on HAART living in challenging socioeconomic areas in South Africa aged 6 months to 8 years and to evaluate the feasibility and preliminary effectiveness of a play-informed, caregiver-implemented, home-based intervention (PICIHBI) for improving play.

Methods:
A feasibility randomized control trial allowed for comparison of PICIHBI and conventional one-on-one occupational therapy interventions. Children were filmed playing pre-, mid-, and postintervention, using the Test of Playfulness (ToP) to assess playfulness. The PICIHBI comprised of 10 monthly sessions facilitated by an occupational therapist, involving group discussions with caregivers and periods of experiential play.

Results:
Twenty-four children with HIV and/or PHE were randomized into one of the two intervention groups. Overall, the group (n = 24) had a median score of 0 (lowest item score) on nine of 24 ToP items and only had a median score of 3 (highest score) on two items. Pre- to postintervention overall ToP scores improved marginally for the PICIHBI group (n = 12) and the conventional group (n = 12). Between-group differences were not significant. The PICIHBI group demonstrated a significant increase in one ToP item score at midassessment. No significant ToP item changes were found in the conventional group.

Conclusion:
Children with HIV were found to have the most difficulty on ToP items relating to the play elements of internal control and freedom from constraints of reality. The PICIHBI did not significantly improve children's play and was not more effective than the conventional intervention. Considerations for feasibility and effectiveness, including barriers to attendance, are discussed.

AIDS Care. 2019 Mar;31(3):275-282. doi: 10.1080/09540121.2018.1533629. Epub 2018 Oct 16. (Open access available)

Interventions for developmental delays in children born to HIV-infected mothers: a systematic review.

McHenry MS, McAteer CI, Oyungu E, Deathe AR, Vreeman RC.
USA, Kenya,

Abstract
Children born to HIV-infected mothers have worse developmental outcomes compared to HIV-unexposed children. However, little is known about interventions to improve developmental outcomes in this population. This study systematically reviews the literature on interventions to improve development in children born to HIV-infected mothers. We systematically searched the following electronic bibliographic databases: Ovid MEDLINE, Embase, PsycINFO, Education Resources Information Center, and the Cochrane Database of Systematic Reviews. Studies were selected on the basis of defined inclusion criteria and excluded if antiretroviral medication was the only intervention. Titles, abstracts, and full texts were assessed by 2 independent reviewers. Data were collected on characteristics of the study design, intervention, and developmental outcomes measured. Risk of bias and strength of evidence were assessed on all included articles. Our search resulted in 11,218 records. After our initial review, 43 records were appraised in their entirety and 9 studies

met all inclusion criteria. **Six were performed in sub-Saharan Africa,** while the remaining 3 were performed in the United States. Eight were randomized-controlled trials and one was a retrospective chart review. Four studies focused on caregiver-training, 2 studied massage therapy, and the remaining studies focused on maternal vitamin supplementation, video-based cognitive therapy, or center-based interventions. **Massage therapy had the most consistent improvements in the domains measured, while caregiver training and cognitive therapy interventions had limited benefits.** The center-based intervention showed no benefit. Only 3 studies had a low risk of bias, and 4 studies had good strength of evidence. Most studies found some benefit. However, these findings are limited by the quality of the study designs, small sample size, and heterogeneity of the interventions and assessments used to measure outcomes. There is a critical need for the creation of evidence-based interventions to promote development in this vulnerable population.

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

J Acquir Immune Defic Syndr. 2019 Jan 1;80(1):56-63. doi: 10.1097/QAI.0000000000001882.
(Open access available)

Effectiveness of a Lay Counselor-Led Combination Intervention for Retention of Mothers and Infants in HIV Care: A Randomized Trial in Kenya.

Fayorsey RN, Wang C, Chege D, Reidy W, Syengo M, Owino SO, Koech E, Sirengo M, Hawken MP, Abrams EJ.
USA, Kenya

BACKGROUND:
Retention of mothers and infants across the prevention of mother-to-child HIV transmission (PMTCT) continuum remains challenging. We assessed the effectiveness of a lay worker administered combination intervention compared with the standard of care (SOC) on mother-infant attrition.

METHODS:
HIV-positive pregnant women starting antenatal care at 10 facilities in western Kenya were randomized using simple randomization **to receive individualized health education, retention/adherence support, appointment reminders, and missed visit tracking vs. routine care per guidelines. The primary endpoint was attrition of mother-infant pairs at 6 months postpartum.** Attrition was defined as the proportion of mother-infant pairs not retained in the clinic at 6 months postpartum because of mother or infant death or lost to follow-up. Intent-to-treat analysis was used to assess the difference in attrition. This trial is registered with ClinicalTrials.gov; NCT01962220.

RESULTS:
From September 2013 to June 2014**, 361 HIV-positive pregnant women were screened, and 340 were randomized to the intervention (n = 170) or SOC (n = 170).** Median age at

enrollment was 26 years (interquartile range 22-30); median gestational age was 24 weeks (interquartile range 17-28). Overall attrition of mother-infant pairs was 23.5% at 6 months postpartum. **Attrition was significantly lower in the intervention arm compared with SOC (18.8% vs. 28.2%, relative risk (RR) = 0.67, 95% confidence interval: 0.45 to 0.99, P = 0.04).** Overall, the proportion of mothers who were retained and virally suppressed (<1000 copies/mL) at 6 months postpartum was 54.4%, with no difference between study arms.

CONCLUSIONS:
Provision of a combination intervention by lay counselors can decrease attrition along the PMTCT cascade in low-resource settings.

PLoS One. 2019 Jun 5;14(6):e0217467. doi: 10.1371/journal.pone.0217467. eCollection 2019.

Impact of male partner involvement on mother-to-child transmission of HIV and HIV-free survival among HIV-exposed infants in rural South Africa: Results from a two phase randomised controlled trial.

Sifunda S[1], Peltzer K[1,2], Rodriguez VJ[3,4,5], Mandell LN[3], Lee TK[6], Ramlagan S[1], Alcaide ML[7], Weiss SM[3], Jones DL[3].
South Africa, United States of America

BACKGROUND:
The Sub-Saharan Africa region still remains the epicentre of the global HIV/AIDS epidemic. With regards to new paediatric HIV infections, almost 90% of new HIV infections are among children (aged 0-14 years), largely through mother to child transmission. Male Partner Involvement in Prevention of Mother to Child Transmission programmes is now strongly advocated as being key in improving infant outcomes. This study describes the role of Male Partner Involvement on infant HIV infection and mortality survival in the first year among HIV-exposed infants born from HIV positive mothers.
METHODS:
This study was a two-phase, two condition (intervention or control) longitudinal study as part of a clinic-randomized Prevention of Mother to Child Transmission controlled trial. For Phase 1, female participants were recruited without their male partners. In Phase 2, both female and male participants were enrolled in the study as couples in order to encourage active Male Partner Involvement during pregnancy. Participants had two assessments prenatally (8-24 weeks and 32 weeks) and three assessments postnatally (6 weeks, 6 months, and 12 months).
RESULTS:
About 1424 women were eligible for recruitment into the study and 18 eligible women declined to participate. All women had a partner; 54% were unmarried, 26% were cohabiting, and 20% were married. Just over half (55%) of the women had been diagnosed with HIV during the current pregnancy. Phase 1 had significantly more HIV-infected infants than Phase 2 at 12-months postpartum (aOR = 4.55 [1.38, 15.07]). Increased depressive symptoms were associated with infant HIV infection at 12-months (aOR = 1.06 [1.01, 1.10]). Phase 1 also had a

significantly greater proportion of dead and HIV-infected infants than Phase 2 at 12-months (aOR = 1.98 [1.33, 2.94]).
CONCLUSION:
Male partner involvement in antenatal care is critical in ensuring infant survival and HIV infection among children born to HIV-positive mothers. This study highlights the high risk of ante-and-post natal depression and underscores the need of screening for depression during pregnancy

HIV vaccine

(see Vaccine – HIV vaccine)

Helminth and other gastrointestinal disorders

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

PLoS Negl Trop Dis. 2019 Jan 31;13(1):e0007085. doi: 10.1371/journal.pntd.0007085. eCollection 2019 Jan. (Open access available)

The long run impact of early childhood deworming on numeracy and literacy: Evidence from Uganda.

Croke K, Atun R.
USA

BACKGROUND:
Up to 1.45 billion people currently suffer from soil transmitted helminth infection, with the largest burden occurring in Africa and Asia. Safe and cost effective deworming treatment exists, but there is a debate about mass distribution of this treatment in high prevalence settings. While the World Health Organization recommends mass administration of anthelmintic drugs for preschool and school-aged children in high (>20%) prevalence settings, and several long run follow up studies of an influential trial have suggested large benefits that persist over time, recent systematic reviews have called this recommendation into question.

METHODS AND FINDINGS:
This paper analyzes the long-term impact of a cluster-randomized trial in eastern Uganda that provided mass deworming treatment to preschool aged children from 2000 to 2003 on the numeracy and literacy skills of children and young adults living in those villages in 2010-2015. This study uses numeracy and literacy data collected seven to twelve years after the end of the deworming trial in a randomly selected subset of communities from the original trial, by an education-focused survey that had no relationship to the deworming study. Building on an earlier working paper which used data from 2010 and 2011 survey rounds, this

paper uses an additional four years of numeracy and literacy data (2012, 2013, 2014, and 2015). Aggregating data from all survey rounds, the difference between numeracy scores in treatment versus control communities is 0.07 standard deviations (SD) (95% CI -0.10, 0.24, p = 0.40), the difference in literacy scores is 0.05 SD (95% CI -0.16, 0.27, p = 0.62), and the difference in total scores is 0.07 SD (95% CI -0.11, 0.25, p = 0.44). There are significant differences in program impact by gender, with numeracy and literacy differentially positively affected for girls, and by age, with treatment effects larger for the primary school aged subsample. There are also significant treatment interactions for those living in households with more treatment-eligible children. There is no evidence of differential treatment effects on age at program eligibility or number of years of program eligibility.

CONCLUSIONS:
Mass deworming of preschool aged children in high prevalence communities in Uganda resulted in no statistically significant gains in numeracy or literacy 7-12 years after program completion. Point estimates were positive but imprecise; the study lacked sufficient power to rule out substantial positive effects or more modest negative effects. However, there is suggestive evidence that deworming was relatively more beneficial for girls, primary school aged children, and children living in households with other treated children.

POTY

BMC Complement Altern Med. 2018 Dec 7;18(1):327. doi: 10.1186/s12906-018-2379-2. (Open access available)

Fortification of Carica papaya fruit seeds to school meal snacks may aid Africa mass deworming programs: a preliminary survey.

Kugo M, Keter L, Maiyo A, Kinyua J, Ndemwa P, Maina G, Otieno P, Songok EM.
Kenya

BACKGROUND:
Soil transmitted helminths (STHs) are among the world's neglected tropical diseases. Morbidity due to STHs is greatest in school-age children who typically have the highest burden of infection. In 2001, WHO passed a resolution for the use of large-scale mass drug administration (MDA) to deworm vulnerable children through school based programs. Though effective, there is concern that MDA might not be sustainable over extended periods. Additionally the current MDA strategy does not consider child malnutrition, a very common malady in resource limited countries. **We report a pilot evaluation of an innovation that bundles school feeding and deworming.**

METHODS:
We designed a maize (corn) flour fortified with grounded dried papaya (Carica papaya) seeds and used it to prepare porridge as per the usual school meal recipe. Children from three primary schools from Nandi County in Kenya were randomized into three arms: One school received 300 ml papaya fortified porridge daily (papaya group), the second school received similar serving of plain porridge without the pawpaw ingredient (control group) and the third school received plain porridge and the conventional MDA approach of one time 400 mg

dosage of albendazole (albendazole arm). Prior to the randomization, an initial baseline stool microscopy analysis was done to determine presence and intensity of intestinal worms. Core indicators of nutrition-height, weight and hemoglobin counts were also assessed. The children were monitored daily for two months and final stool sample analysis and clinical monitoring done at the end of the study. Baseline and follow-up data were analyzed and compared through SAS version 9.1 statistical package.

RESULTS:
A total of 326 children participated in the trial. The overall prevalence of Ascaris lumbricoides was 29.4% (96), Trichuris Trichura 5.2% (17) and hookworm 1 (0.3%). Papaya seed fortified porridge reduced the Ascaris lumbricoides egg count by 63.9% after the two month period (mean 209.7epg to 75.7 $p < 0.002$) as compared to the albendazole arm 78.8% (129.5 epg to 27.5, p value 0.006). The control group showed an increase in egg count (42.epg to 56.3) though it was not statistically significant. Hemoglobin counts in the papaya group increased from a mean of 2 g/dL (11.5 g/dL to 13.5 g/dL, $p < 0.001$), as compared to the albendazole arm that increased by 1 g/dL (12.8-13.9, $p < 0.001$). No significant change was observed in the placebo arm (13.2 to 13.1). Interestingly the papaya group showed a significant reduction of children with Tinea capitis (ringworms) (54.4 to 34%, $p < 0.002$) as compared to the albendazole arm that showed an increase in ringworm infestation though not statistically significant (39.7 to 64.7% $p = 0.608$).

CONCLUSION:
Papaya seed fortified porridge had a significant effect on reduction of Ascaris lumbricoides burden. It had a better nutritional outcome and effect on child fungal infections than albendazole. Its application as a routine school meal may aid current national school based nutrition and deworming programs in Africa.

PLoS Negl Trop Dis. 2018 Aug 9;12(8):e0006620. doi: 10.1371/journal.pntd.0006620. eCollection 2018 Aug. (Open access available)

Dynamic changes in human-gut microbiome in relation to a placebo-controlled anthelminthic trial in Indonesia.

Martin I, Djuardi Y, Sartono E, Rosa BA, Supali T, Mitreva M, Houwing-Duistermaat JJ, Yazdanbakhsh M.
Indonesia, The Netherlands, USA, UK

BACKGROUND:
Microbiome studies suggest the presence of an interaction between the human gut microbiome and soil-transmitted helminth. Upon deworming, a complex interaction between the anthelminthic drug, helminths and microbiome composition might occur. To dissect this, we analyse the changes that take place in the gut bacteria profiles in samples from a double blind placebo controlled trial conducted in an area endemic for soil transmitted helminths in Indonesia.

METHODS:

Either placebo or albendazole were given every three months for a period of one and a half years. Helminth infection was assessed before and at 3 months after the last treatment round. In 150 subjects, the bacteria were profiled using the 454 pyrosequencing. Statistical analysis was performed cross-sectionally at pre-treatment to assess the effect of infection, and at post-treatment to determine the effect of infection and treatment on microbiome composition using the Dirichlet-multinomial regression model.

RESULTS:
At a phylum level, at pre-treatment, no difference was seen in microbiome composition in terms of relative abundance between helminth-infected and uninfected subjects and at post-treatment, no differences were found in microbiome composition between albendazole and placebo group. However, in subjects who remained infected, there was a significant difference in the microbiome composition of those who had received albendazole and placebo. This difference was largely attributed to alteration of Bacteroidetes. Albendazole was more effective against Ascaris lumbricoides and hookworms but not against Trichuris trichiura, thus in those who remained infected after receiving albendazole, the helminth composition was dominated by T. trichiura.

DISCUSSION:
We found that overall, albendazole does not affect the microbiome composition. However, there is an interaction between treatment and helminths as in subjects who received albendazole and remained infected there was a significant alteration in Bacteroidetes. This helminth-albendazole interaction needs to be studied further to fully grasp the complexity of the effect of deworming on the microbiome.

PLoS Negl Trop Dis. 2019 Feb 11;13(2):e0007180. doi: 10.1371/journal.pntd.0007180. eCollection 2019 Feb. (Open access available)

Effect of a sanitation intervention on soil-transmitted helminth prevalence and concentration in household soil: A cluster-randomized controlled trial and risk factor analysis.

Steinbaum L, Mboya J, Mahoney R, Njenga SM, Null C, Pickering AJ.
USA, Kenya

Abstract
Improved sanitation has been associated with a reduced prevalence of soil-transmitted helminth (STH) infection and has been hypothesized to prevent fecal contamination from spreading throughout the household environment. **We evaluated the effect of providing households with a pit latrine with a plastic slab and drophole cover, child feces management tools, and associated behavioral messaging on reducing STH eggs in household soil**. We collected soil samples from 2107 households (898 control and 1209 improved sanitation intervention households) that were enrolled in the WASH Benefits cluster randomized controlled trial in rural Kenya and performed a post-intervention

analysis after two years of intervention exposure. Following a pre-specified analysis plan, we combined all households that received the sanitation intervention into one group for comparison to control households. **The prevalence of STH eggs in soil was 18.9% in control households and 17.0% in intervention households.** The unadjusted prevalence ratio of total STH eggs in the intervention groups compared to the control group was 0.94 (95% CI: 0.78-1.13). The geometric mean concentration was 0.05 eggs/g dry soil in control households and intervention households. Unadjusted and adjusted models gave similar results. **We found use of a shared latrine, presence of a roof over the sampling area, and the number of dogs owned at baseline was associated with an increased prevalence of STH eggs in soil; the presence of a latrine that was at least 2 years old and a latrine with a covered drophole was associated with a reduction in the prevalence of STH eggs in soil.** Soil moisture content was also associated with an increased prevalence of STH eggs in soil. **Our results indicate that an intervention designed to increase access to improved latrines and child feces management tools may not be enough to impact environmental occurrence of STH in endemic areas where latrine coverage is already high.**

Lancet. 2019 Apr 18. pii: S0140-6736(18)32591-1. doi: 10.1016/S0140-6736(18)32591-1. (Open access available)

Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial.

Pullan RL, Halliday KE, Oswald WE, Mcharo C, Beaumont E, Kepha S, Witek-McManus S, Gichuki PM, Allen E, Drake T, Pitt C, Matendechero SH, Gwayi-Chore MC, Anderson RM, Njenga SM, Brooker SJ, Mwandawiro CS.
Kenya

BACKGROUND:
School-based deworming programmes can reduce morbidity attributable to soil-transmitted helminths in children but do not interrupt transmission in the wider community. We assessed the effects of alternative mass treatment strategies on community soil-transmitted helminth infection.

METHODS:
In this cluster-randomised controlled trial, 120 community units (clusters) serving 150 000 households in Kenya were randomly assigned (1:1:1) to receive albendazole through annual school-based treatment targeting 2-14 year olds or annual or biannual community-wide treatment targeting all ages. The primary outcome was community hookworm prevalence, assessed at 12 and 24 months through repeat cross-sectional surveys. Secondary outcomes were Ascaris lumbricoides and Trichuris trichiura prevalence, infection intensity of each soil-transmitted helminth species, and treatment coverage and costs. Analysis was by intention to treat.

FINDINGS:

After 24 months, prevalence of hookworm changed from 18·6% (95% CI 13·9-23·2) to 13·8% (10·5-17·0) in the annual school-based treatment group, 17·9% (13·7-22·1) to 8·0% (6·0-10·1) in the annual community-wide treatment group, and 20·6% (15·8-25·5) to 6·2% (4·9-7·5) in the biannual community-wide treatment group. **Relative to annual school-based treatment, the risk ratio for annual community-wide treatment was 0·59 (95% CI 0·42-0·83; p<0·001) and for biannual community-wide treatment was 0·46 (0·33-0·63; p<0·001).** More modest reductions in risk were observed after 12 months. Risk ratios were similar across demographic and socioeconomic subgroups after 24 months. No adverse events related to albendazole were reported.

INTERPRETATION:
Community-wide treatment was more effective in reducing hookworm prevalence and intensity than school-based treatment, with little additional benefit of treating every 6 months, and was shown to be remarkably equitable in coverage and effects.

Hepatitis

Injury prevention

Integrated management of Childhood Illness (IMCI)

Iodine deficiency

Kidney disease

POTY
Pediatr Nephrol. 2019 May;34(5):829-835. doi: 10.1007/s00467-018-4071-7. Epub 2018 Sep 7. (Open access available)
Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial.
Yadav M, Sinha A, Khandelwal P, Hari P, Bagga A.
India

BACKGROUND:
While patients with frequently relapsing nephrotic syndrome (FRNS) are initially treated with long-term alternate-day prednisolone, relapses and adverse effects are common. In an open-label randomized controlled trial, we compared the efficacy of therapy with low-dose daily to standard alternate-day prednisolone in reducing relapse rates over 12-month follow-up.

METHODS:
Consecutive patients, aged 2-18 years, with FRNS were included. Following therapy of relapse, prednisolone was tapered to 0.75 mg/kg on alternate days. **Stratifying for steroid dependence, patients were randomly assigned to prednisolone at 0.2-0.3 mg/kg daily or 0.5-0.7 mg/kg alternate day for 12 months**. Relapses were treated with daily prednisolone, followed by return to intervention. Primary outcome was the incidence of relapses. Proportion with therapy failure (≥ 2 relapses in any 6 months or significant steroid toxicity) and sustained remission, cumulative prednisolone intake and adverse events were evaluated.

RESULTS:
Patients receiving daily prednisolone (n = 30) showed significantly fewer relapses than those on alternate-day therapy (n = 31) (0.55 relapses/person-year versus 1.94 relapses/person-year; incidence rate ratio 0.28; 95% CI 0.15, 0.52). Daily therapy was associated with higher rates of sustained remission at 6 months (73.3 versus 48.4%) and 1 year (60 versus 31.6%; log rank p = 0.013), lower rates of treatment failure at 6 months (3.3 versus 32.8%) and 1 year (6.7 versus 57.4%; p < 0.0001), and lower prednisolone use (0.27 ± 0.07 versus 0.39 ± 0.19 mg/kg/day; p = 0.003). Three and two patients need to receive the study intervention to enable sustained remission and prevent treatment failure, respectively.

CONCLUSIONS:
In patients with FRNS, daily administration of low-dose prednisolone is more effective than standard-dose alternate day therapy in lowering relapse rates, sustaining remission, and enabling steroid sparing.

Kidney Int. 2019 Jan;95(1):210-218. doi: 10.1016/j.kint.2018.08.039. Epub 2018 Nov 26.

Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial.

Sinha A, Puraswani M, Kalaivani M, Goyal P, Hari P, Bagga A.
India

Abstract
Both levamisole and mycophenolate mofetil (MMF) prevent relapses in patients with frequently relapsing nephrotic syndrome; however, their efficacy has not been compared prospectively. This single-center, randomized, open-label trial enrolled 149 children ages 6-18 years with frequently relapsing or steroid-dependent nephrotic syndrome. Participants were randomized in a 1:1 ratio to receive therapy with MMF (750-1000 mg/m daily) or levamisole (2-2.5 mg/kg on alternate days) for 1 year; prednisolone was discontinued by 2-3 months. In intention-to-treat analyses, the frequency of relapse was similar between participants treated with MMF and levamisole (mean difference -0.29 relapses/patient-year; 95% confidence interval -0.65, 0.08). Relapse rates declined to almost one-third of baseline for both treatment groups. Therapy with MMF was not superior to levamisole in terms of the

proportions of participants with sustained remission (40.8% vs. 34.2%), frequent relapses (14.5% vs. 16.4%), or treatment failure, a composite outcome of frequent relapses, steroid resistance, or significant steroid toxicity (15.8% vs. 20.6%). These outcomes were also similar in time to event analyses. Changes in anthropometry and blood pressure were similar between the groups, and the rates of adverse effects were low in both groups. Flow cytometry in 32 participants demonstrated similar proportions of B cells and CD4+, CD8+, T helper (Th)1, Th2, Th17, and T regulatory (Treg) cells during follow-up. Therapy with MMF was not superior to levamisole in the frequency of relapses, likelihood of sustained remission or corticosteroid sparing in children with frequently relapsing or steroid-dependent nephrotic syndrome.

Paediatr Int Child Health. 2018 Nov;38(4):251-260. doi: 10.1080/20469047.2018.1505589. Epub 2018 Aug 9. (Open access available)

Three-monthly bolus vitamin D supplements (1000 vs 400 IU/day) for prevention of bone loss in children with difficult-to-treat nephrotic syndrome: a randomised clinical trial.

Singh DN, Krishnamurthy S, Kamalanathan SK, Harichandrakumar KT, Sivamurukan P.
India

BACKGROUND:
Nephrotic syndrome (NS) in children is one of the most common chronic diseases with a remitting and relapsing course. Glucocorticoids (prednisolone) are considered to be the treatment of choice but are associated with osteoporosis. There are no uniform consensus guidelines regarding the optimum dose of calcium and vitamin D for osteoprotection. Some authorities suggest a daily dose of 1000 IU vitamin D for children for osteoprotection, while others suggest a daily dose of 400 IU.
OBJECTIVES:
To compare the efficacy of three-monthly bolus vitamin D supplementation (1000 vs 400 IU/day) to prevent bone loss in children with difficult-to-treat NS (DTNS).

METHODS:
In this parallel-group, open-label, randomised clinical trial, 60 children aged 1-18 years with DTNS [37 with frequently relapsing NS (FRNS), 13 steroid-dependent NS (SDNS) and 10 steroid-resistant NS (SRNS)] were enrolled and block randomised in a 1:1 allocation ratio to receive 1000 IU/day vitamin D (Group A, n = 30) or 400 IU/day (Group B, n = 30), administered as three-monthly bolus supplemental doses. In Group A, vitamin D (cholecalciferol, Calcirol®sachet) was administered as a stat dose of 90,000 IU every three months (calculated for a period of three months at 1000 IU/day). In Group B, vitamin D (cholecalciferol) was administered as a stat dose of 36,000 IU every three months (calculated for a period of three months at 400 IU/day). **The proportionate change in bone mineral content (BMC) was studied by dual energy X-ray absorptiometry (DEXA) scan in both groups after vitamin D supplementation by analysing the values of BMC obtained 12 months apart** (baseline vs. after 12 months).

RESULTS:
Sixty children were randomised to receive vitamin D at a dose of either 1000 IU/day (Group A) or 400 IU/day (Group B). The two groups were comparable in their baseline clinical and laboratory parameters (including BMC and bone mineral density (BMD)). The distribution of the three types of NS (FRNS, SDNS and SRNS) was also comparable in both groups. In Group A, there were 19, 6 and 5 children with FRNS, SDNS and SRNS, respectively, and in Group B there were 18, 7 and 5 children with FRNS, SDNS and SRNS, respectively. **The proportionate change in BMC was not significantly different between the two groups (median proportionate change in BMC in Group A 13.36% vs 11.59% in Group B, p = 0.22).** Overall, BMC increased in both groups (96.7% in each). Only one (3.3%) patient in each group exhibited bone loss. None of the patients had a urinary calcium:creatinine ratio >0.2 at the end of the study.

CONCLUSION:
Three-monthly bolus vitamin D dosing regimens administered either as 1000 or 400 IU/day prevent bone loss in children with DTNS who require long-term steroids. **Overall, three-monthly bolus supplemental prophylactic vitamin D, either 1000 or 400 IU/day, would seem to be an effective strategy for preventing bone loss in children with DTNS**, as evidenced by the extremely low rates of bone loss (3.3% in each group), and is useful for delivering optimal care to children with DTNS. However, since this study was designed as an equivalence trial and not a superiority trial, further studies are required to demonstrate the superiority of the former regimen over the latter.

Leishmaniasis

PLoS Negl Trop Dis. 2019 Mar 4;13(3):e0007193. doi: 10.1371/journal.pntd.0007193. eCollection 2019 Mar. (Open access available)

Insecticide-impregnated dog collars reduce infantile clinical visceral leishmaniasis under operational conditions in NW Iran: A community-wide cluster randomised trial.

Courtenay O, Bazmani A, Parvizi P, Ready PD, Cameron MM.

OBJECTIVE:
To assess the effectiveness of community-wide deployment of insecticide-impregnated collars for dogs- the reservoir of Leishmania infantum-to reduce infantile clinical visceral leishmaniasis (VL).

METHODS:
A pair matched-cluster randomised controlled trial involving 40 collared and 40 uncollared control villages (161 [95% C.L.s: 136, 187] children per cluster), was designed to detect a 55% reduction in 48 month confirmed VL case incidence. The intervention study was designed by

the authors, but implemented by the Leishmaniasis Control Program in NW Iran, from 2002 to 2006.

RESULTS:
The collars provided 50% (95% C.I. 17·8%-70·0%) protection against infantile VL incidence (0·95/1000/yr compared to 1·75/1000/yr). Reductions in incidence were observed across 76% (22/29) of collared villages compared to pair-matched control villages, with 31 fewer cases by the end of the trial period. In 11 paired villages, no further cases were recorded post-intervention, whereas in 7 collared villages there were 9 new clinical cases relative to controls. Over the trial period, 6,835 collars were fitted at the beginning of the 4 month sand fly season, of which 6.9% (95% C.I. 6.25%, 7.56%) were lost but rapidly replaced. Collar coverage (percent dogs collared) per village varied between 66% and 100%, with a mean annual coverage of 87% (95% C.I. 84·2, 89·0%). The variation in post-intervention clinical VL incidence was not associated with collar coverage, dog population size, implementation logistics, dog owner compliance, or other demographic variables tested. Larger reductions and greater persistence in incident case numbers (indicative of transmission) were observed in villages with higher pre-existing VL case incidence.

CONCLUSION:
Community-wide deployment of collars can provide a significant level of protection against infantile clinical VL, achieved in this study by the local VL Control Program, demonstrating attributes desirable of a sustainable public health program. The effectiveness is not dissimilar to the community-level protection provided against human and canine infection with L. infantum.

Lymphatic filariasis

Leprosy

Malaria

Malaria diagnosis

PLoS Med. 2018 Jul 17;15(7):e1002607. doi: 10.1371/journal.pmed.1002607. eCollection 2018 Jul. (Open access available)

Improving rational use of ACTs through diagnosis-dependent subsidies: Evidence from a cluster-randomized controlled trial in western Kenya.

Prudhomme O'Meara W, Menya D, Laktabai J, Platt A, Saran I, Maffioli E, Kipkoech J, Mohanan M, Turner EL.

USA, Kenya

Abstract
BACKGROUND:
More than half of artemisinin combination therapies (ACTs) consumed globally are dispensed in the retail sector, where diagnostic testing is uncommon, leading to overconsumption and poor targeting. In many malaria-endemic countries, ACTs sold over the counter are available at heavily subsidized prices, further contributing to their misuse. Inappropriate use of ACTs can have serious implications for the spread of drug resistance and leads to poor outcomes for nonmalaria patients treated with incorrect drugs. We evaluated the public health impact of an innovative strategy that targets ACT subsidies to confirmed malaria cases by coupling free diagnostic testing with a diagnosis-dependent ACT subsidy.

METHODS AND FINDINGS:
We conducted a **cluster-randomized controlled trial in 32 community clusters in western Kenya (population approximately 160,000).** Eligible clusters had retail outlets selling ACTs and existing community health worker (CHW) programs and were randomly assigned 1:1 to control and intervention arms. **In intervention areas, CHWs were available in their villages to perform malaria rapid diagnostic tests (RDTs) on demand for any individual >1 year of age experiencing a malaria-like illness. Malaria RDT-positive individuals received a voucher for a discount on a quality-assured ACT, redeemable at a participating retail medicine outlet. In control areas, CHWs offered a standard package of health education, prevention, and referral services.** We conducted 4 population-based surveys-at baseline, 6 months, 12 months, and 18 months-of a random sample of households with fever in the last 4 weeks to evaluate predefined, individual-level outcomes. **The primary outcome was uptake of malaria diagnostic testing at 12 months. The main secondary outcome was rational ACT use, defined as the proportion of ACTs used by test-positive individuals**. Analyses followed the intention-to-treat principle using generalized estimating equations (GEEs) to account for clustering with prespecified adjustment for gender, age, education, and wealth. All descriptive statistics and regressions were weighted to account for sampling design. **Between July 2015 and May 2017, 32,404 participants were tested for malaria, and 10,870 vouchers were issued. A total of 7,416 randomly selected participants with recent fever from all 32 clusters were surveyed.** The majority of recent fevers were in children under 18 years (62.9%, n = 4,653). The gender of enrolled participants was balanced in children (49.8%, n = 2,318 boys versus 50.2%, n = 2,335 girls), but more adult women were enrolled than men (78.0%, n = 2,139 versus 22.0%, n = 604). **At baseline, 67.6% (n = 1,362) of participants took an ACT for their illness, and 40.3% (n = 810) of all participants took an ACT purchased from a retail outlet.** At 12 months, 50.5% (n = 454) in the intervention arm and 43.4% (n = 389) in the control arm had a malaria diagnostic test for their recent fever (adjusted risk difference [RD] = 9 percentage points [pp]; 95% CI 2-15 pp; p = 0.015; adjusted risk ratio [RR] = 1.20; 95% CI 1.05-1.38; p = 0.015). By 18 months, the ARR had increased to 1.25 (95% CI 1.09-1.44; p = 0.005). **Rational use of ACTs in the intervention area increased from 41.7% (n = 279) at baseline to 59.6% (n = 403) and was 40% higher in the intervention arm at 18 months (ARR 1.40; 95% CI 1.19-1.64; p < 0.001).** While intervention effects increased between 12 and 18 months, we were not able to estimate

longer-term impact of the intervention and could not independently evaluate the effects of the free testing and the voucher on uptake of testing.

CONCLUSIONS:
Diagnosis-dependent ACT subsidies and community-based interventions that include the private sector can have an important impact on diagnostic testing and population-wide rational use of ACTs. Targeting of the ACT subsidy itself to those with a positive malaria diagnostic test may also improve sustainability and reduce the cost of retail-sector ACT subsidies.

Insecticide-treated bed nets

Lancet. 2018 Aug 18;392(10147):569-580. doi: 10.1016/S0140-6736(18)31711-2. Epub 2018 Aug 10. (Open access available)

Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial.

Tiono AB, Ouédraogo A, Ouattara D, Bougouma EC, Coulibaly S, Diarra A, Faragher B, Guelbeogo MW, Grisales N, Ouédraogo IN, Ouédraogo ZA, Pinder M, Sanon S, Smith T, Vanobberghen F, Sagnon N, Ranson H, Lindsay SW.
Burkina Faso, UK, Switzerland

BACKGROUND:
Substantial reductions in malaria incidence in sub-Saharan Africa have been achieved with massive deployment of long-lasting insecticidal nets (LLINs), but pyrethroid resistance threatens control. Burkina Faso is an area with intense malaria transmission and highly pyrethroid-resistant vectors. **We assessed the effectiveness of bednets containing permethrin, a pyrethroid, and pyriproxyfen, an insect growth regulator, versus permethrin-only (standard) LLINs against clinical malaria in children younger than 5 years in Banfora, Burkina Faso.**

METHODS:
In this two-group, step-wedge, cluster-randomised, controlled, superiority trial, standard LLINs were incrementally replaced with LLINs treated with permethrin plus pyriproxyfen (PPF) in 40 rural clusters in Burkina Faso. In each cluster, 50 children (aged 6 months to 5 years) were followed up by passive case detection for clinical malaria. Cross-sectional surveys were done at the start and the end of the transmission seasons in 2014 and 2015. We did monthly collections from indoor light traps to estimate vector densities. Primary endpoints were the incidence of clinical malaria, measured by passive case detection, and the entomological inoculation rate. Analyses were adjusted for clustering and for month and health centre. This trial is registered as ISRCTN21853394.

FINDINGS:
1980 children were enrolled in the cohort in 2014 and 2157 in 2015. At the end of the study, more than 99% of children slept under a bednet. The incidence of clinical malaria was 2·0 episodes per child-year in the standard LLIN group and 1·5 episodes per child-year in the PPF-treated LLIN group (incidence rate ratio 0·88 [95% CI 0·77-0·99; p=0·04]). The entomological inoculation rate was 85 (95% CI 63-108) infective bites per transmission season in the standard LLIN group versus 42 (32-52) infective bites per transmission season in the PPF-treated LLIN group (rate ratio 0·49, 95% CI 0·32-0·66; p<0·0001).

INTERPRETATION:
PPF-treated LLINs provide greater protection against clinical malaria than do standard LLINs and could be used as an alternative to standard LLINs in areas with intense transmission of Plasmodium falciparum malaria and highly pyrethroid-resistant vectors.

Cochrane Database Syst Rev. 2018 Nov 6;11:CD000363. doi: 10.1002/14651858.CD000363.pub3. (Open access available)

Insecticide-treated nets for preventing malaria.

Pryce J, Richardson M, Lengeler C.
UK

BACKGROUND:
A previous version of this Cochrane Review identified that insecticide-treated nets (ITNs) are effective at reducing child mortality, parasite prevalence, and uncomplicated and severe malaria episodes. Insecticide-treated nets have since become a core intervention for malaria control and have contributed greatly to the dramatic decline in disease incidence and malaria-related deaths seen since the turn of the millennium. **However, this time period has also seen a rise in resistance to pyrethroids (the insecticide used in ITNs), raising questions over whether the evidence from trials conducted before resistance became widespread can be applied to estimate the impact of ITNs on malaria transmission today.**

OBJECTIVES:
The primary objective of this review was to assess the impact of ITNs on mortality and malaria morbidity, incorporating any evidence published since the previous update into new and existing analyses, and assessing the certainty of the resulting evidence using GRADE.

SEARCH METHODS:
We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) published in the Cochrane Library, MEDLINE, Embase, LILACS, the World Health Organization (WHO) International Clinical Trials Registry Platform, ClinicalTrials.gov, and the ISRCTN registry for new trials published since 2004 and up to 18 April 2018.

SELECTION CRITERIA:
We included individual randomized controlled trials (RCTs) and cluster RCTs comparing bed nets or curtains treated with a synthetic pyrethroid insecticide at a minimum target impregnation dose recommended by the WHO with no nets or untreated nets.

DATA COLLECTION AND ANALYSIS:
One review author assessed the identified trials for eligibility and risk of bias, and extracted data. We compared intervention and control data using risk ratios (RRs), rate ratios, and mean differences, and presented all results with their associated 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach. **We drew on evidence from a meta-analysis of entomological outcomes stratified by insecticide resistance from 2014 to inform the GRADE assessments.**

MAIN RESULTS:
Our updated search identified three new trials. A total of 23 trials met the inclusion criteria, enrolling more than 275,793 adults and children. The included studies were conducted between 1987 and 2001.ITN versus no netsInsecticide-treated nets reduce child mortality from all causes by 17% compared to no nets (rate ratio 0.83, 95% CI 0.77 to 0.89; 5 trials, 200,833 participants, high-certainty evidence). This corresponds to a saving of 5.6 lives (95% CI 3.6 to 7.6) each year for every 1000 children protected with ITNs. Insecticide-treated nets also reduce the incidence of uncomplicated episodes of Plasmodium falciparum malaria by almost a half (rate ratio 0.55, 95% CI 0.48 to 0.64; 5 trials, 35,551 participants, high-certainty evidence) and probably reduce the incidence of uncomplicated episodes of Plasmodium vivax malaria (risk ratio (RR) 0.61, 95% CI 0.48 to 0.77; 2 trials, 10,967 participants, moderate-certainty evidence).Insecticide-treated nets were also shown to reduce the prevalence of P falciparum malaria by 17% compared to no nets (RR 0.83, 95% CI 0.71 to 0.98; 6 trials, 18,809 participants, high-certainty evidence) but may have little or no effect on the prevalence of P vivax malaria (RR 1.00, 95% CI 0.75 to 1.34; 2 trials, 10,967 participants, low-certainty evidence). A 44% reduction in the incidence of severe malaria episodes was seen in the ITN group (rate ratio 0.56, 95% CI 0.38 to 0.82; 2 trials, 31,173 participants, high-certainty evidence), as well as an increase in mean haemoglobin (expressed as mean packed cell volume) compared to the no-net group (mean difference 1.29, 95% CI 0.42 to 2.16; 5 trials, 11,489 participants, high-certainty evidence). ITN versus untreated netsInsecticide-treated nets probably reduce child mortality from all causes by a third compared to untreated nets (rate ratio 0.67, 95% CI 0.36 to 1.23; 2 trials, 25,389 participants, moderate-certainty evidence). This corresponds to a saving of 3.5 lives (95% CI -2.4 to 6.8) each year for every 1000 children protected with ITNs. Insecticide-treated nets also reduce the incidence of uncomplicated P falciparum malaria episodes (rate ratio 0.58, 95% CI 0.44 to 0.78; 5 trials, 2036 participants, high-certainty evidence) and may also reduce the incidence of uncomplicated P vixax malaria episodes (rate ratio 0.73, 95% CI 0.51 to 1.05; 3 trials, 1535 participants, low-certainty evidence).Use of an ITN probably reduces P falciparum prevalence by one-tenth in comparison to use of untreated nets (RR 0.91, 95% CI 0.78 to 1.05; 3 trials, 2,259 participants, moderate-certainty evidence). However, based on the current evidence it is unclear whether or not ITNs impact on P vivax prevalence (1 trial, 350 participants, very low certainty evidence) or mean packed cell volume (2 trials, 1,909 participants, low certainty evidence).

AUTHORS' CONCLUSIONS:
Although there is some evidence that insecticide resistance frequency has some effects on mosquito mortality, it is unclear how quantitatively important this is. It appeared insufficient to downgrade the strong evidence of benefit on mortality and malaria illness from the trials conducted earlier.

Intermittent preventative treatment and seasonal malaria prophylaxis

PLoS One. 2019 Feb 6;14(2):e0210789. doi: 10.1371/journal.pone.0210789. eCollection 2019. (Open access available)

Adherence to intermittent preventive treatment for malaria in Papua New Guinean infants: A pharmacological study alongside the randomized controlled trial.

Sottas O, Guidi M, Thieffry B, Schneider M, Décosterd L, Mueller I, Genton B, Csajka C, Senn N. Switzerland, Australia, Papua New Guinea

BACKGROUND:
The intermittent preventive treatment in infants (IPTi) trial that took place in Papua New Guinea showed an overall reduction of 29% of the risk of malaria when delivering single-dose sulfadoxine-pyrimethamine (SP) associated to 3 days of amodiaquine (AQ) every three months to children during the first year of life. The aim of the present study was to assess if the last two doses of AQ were truly administered as prescribed by the parents at home based on drug level measurement and PK modelling, which is a good proxy of medication adherence. It provides also important information to discuss the efficacy of the intervention and on feasibility of self-administered preventive malaria treatment.

METHODS AND FINDINGS:
During the three-arm randomized double-blinded IPTi trial, each child was prescribed one dose of SP (day 0) and 3 doses of either AQ or artesunate (AS) at day 0, 1 & 2 adjusted to weight or placebo. Treatments were given at 3, 6, 9 and 12 months of age. **The first day of treatment was delivered by nursing staff (initiation under directly observed treatment (DOT)) and the two last doses of AQ or AS by parents at home without supervision.** For this cross-sectional study, **206 consecutive children already involved in the IPTi trial were enrolled over a 2-month period.** At the time of the survey, allocation of the children to one of the three arms was not known. Blood samples for drug level measurement were collected from finger pricks one day after the planned last third dose intake. Only children allocated to the SP-AQ arm were included in the present analysis. Indeed, the half-life of AS is too short to assess if drugs were given on not. Because of the short half-life of AQ, desethyl-AQ (metabolite of AQ (DAQ)) measurements were used to investigate AQ medication adherence. Two PK (PK) models from previously published studies in paediatric populations were

applied to the dataset using non-linear mixed effect modelling (NONMEM) to estimate the number of doses really given by the parents. The study nurse reported the administration time for the first AQ dose while it was estimated by the parents for the remaining two doses. Out of 206 children, 64 were in the SP-AQ arm. The adjusted dosing history for each individual was identified as the one with the lowest difference between observed and individual predicted concentrations estimated by the two PK models for all the possible adherence schemes. The median (range) blood concentration AQ in AQ arm was 9.3 ng/mL (0-1427.8 ng/mL), (Quartiles 1-3: 2.4 ng/mL -22.2 ng/mL). The median (range) for DAQ was 162.0 ng/mL (0-712 ng/mL), (Quartiles 1-3: 80.4 ng/mL-267.7 ng/mL). Under the assumption of full adherence for all participants, a marked underprediction of concentrations was observed using both PK models. **Our results suggest that only 39-50% of children received the three scheduled doses of AQ as prescribed, 33-37% two doses and 17-24% received only the first dose administered by the study nurse.** Both models were highly congruent to classify adherence patterns.

CONCLUSIONS:
Considering the IPTi intervention, our results seem to indicate that medication adherence is low in the ideal trial research setting and is likely to be even lower if given in day-to-day practice, questioning the real impact that this intervention might have. More generally, the estimation of the number of doses truly administered, a proxy measure of adherence and an assessment of the feasibility of the mode of administration, should be more thoroughly studied when discussing the efficacy of the interventions in trials investigating self-administered malaria preventive treatments.

BMC Health Serv Res. 2018 Dec 19;18(1):984. doi: 10.1186/s12913-018-3791-5. (Open access available)

Introducing post-discharge malaria chemoprevention (PMC) for management of severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation.

Nkosi-Gondwe T, Robberstad B, Blomberg B, Phiri KS, Lange S.
Norway, Malawi

BACKGROUND:
Severe malarial anaemia is one of the leading causes of paediatric hospital admissions in Malawi. Post-discharge malaria chemoprevention (PMC) is the intermittent administration of full treatment courses of antimalarial to children recovering from severe anaemia and findings suggest that this intervention significantly reduces readmissions and deaths in these children. Community delivery of health interventions utilizing community health workers (CHWs) has been successful in some programmes and not very positive in others. In Malawi, there is an on-going cluster randomised trial that aims to find the optimum strategy for delivery of dihydroartemesinin-piperaquine (DHP) for PMC in children with severe anaemia. Our qualitative study aimed to explore the feasibility of utilizing CHWs also known as health

surveillance assistants (HSAs) to remind caregivers to administer PMC medication in the existing Malawian health system.

METHODS:
Between December 2016 and March 2018, 20 individual in-depth-interviews (IDIs) and 2 focus group discussions (FGDs) were conducted with 39 HSAs who had the responsibility of conducting home visits to remind caregivers of children who were prescribed PMC medication in the trial. All interviews were conducted in the local language, transcribed verbatim, and translated into English. The transcripts were uploaded to NVIVO 11 and analysed using the thematic framework analysis method.

RESULTS:
Although intrinsic motivation was reportedly high, adherence to the required number of home visits was very poor with only 10 HSAs reporting full adherence. Positive factors for adherence were the knowledge and perception of the effectiveness of PMC and the recognition from the community as well as health system. Poor training, lack of supervision, high workload, as well as technical and structural difficulties; were reported barriers to adherence by the HSAs.

CONCLUSIONS:
Post-discharge malaria chemoprevention with DHP is perceived as a positive approach to manage children recovering from severe anaemia by HSAs in Malawi. However, adherence to home visit reminders was very poor and the involvement of HSAs in a scale up of this intervention may pose a challenge in the existing Malawian health system.

TRIAL REGISTRATION:
ClinicalTrials.gov identifier NCT02721420 . The trial was registered on 26 March 2016.

KEYWORDS:
Anaemia; Community health workers; Malaria; Malawi; Secondary prevention; Social perception

BMC Health Serv Res. 2018 Jul 11;18(1):544. doi: 10.1186/s12913-018-3327-z. (Open access available)

Post-discharge malaria chemoprevention (PMC) in Malawi: caregivers` acceptance and preferences with regard to delivery methods.

Svege S, Kaunda B, Robberstad B, Nkosi-Gondwe T, Phiri KS, Lange S.
Norway, Malawi

BACKGROUND:
In malaria endemic countries of sub-Saharan Africa, many children develop severe anaemia due to previous and current malaria infections. After blood transfusions and antimalarial treatment at the hospital they are usually discharged without any follow-up. In the post-

discharge period, these children may contract new malaria infections and develop rebound severe anaemia. **A randomised placebo-controlled trial in Malawi showed 31% reduction in malaria- and anaemia-related deaths or hospital readmissions among children under 5 years of age given antimalarial drugs for 3 months post-discharge.** Thus, post-discharge malaria chemoprevention (PMC) may provide substantial protection against malaria and anaemia in young children living in areas of high malaria transmission. A delivery implementation trial is currently being conducted in Malawi to determine the optimal strategy for PMC delivery. In the trial, PMC is delivered through community- or facility-based methods with or without the use of reminders via phone text message or visit from a Health Surveillance Assistant. This paper describes the acceptance of PMC among caregivers.

METHODS:
From October to December 2016, 30 in-depth interviews and 5 focus group discussions were conducted with caregivers of children who recently completed the last treatment course in the trial. Views on the feasibility of various delivery methods and reminder strategies were collected. The interviews were transcribed verbatim, translated to English, and coded using the software programme NVivo.

RESULTS:
Community-based delivery was perceived as more favourable than facility-based delivery due to easy home access to drugs and fewer financial concerns. Many caregivers reported lack of visits from Health Surveillance Assistants and preferred text message reminders sent directly to their phones rather than waiting on these visits. Positive attitudes towards active use of health cards for remembering treatment dates were especially evident. Additionally, caregivers shared positive experiences from participation in the programme and described dihydroartemisinin-piperaquine as a safe and effective antimalarial drug that improved the health and well-being of their children.

CONCLUSIONS:
Post-discharge malaria chemoprevention given to children under the age of 5 previously treated for severe anaemia is highly accepted among caregivers. Caregivers prefer community-based delivery with use of health cards as their primary tool of reference.

PLoS Med. 2019 Mar 13;16(3):e1002762. doi: 10.1371/journal.pmed.1002762. eCollection 2019 Mar. (Open access available)

Seasonal malaria chemoprevention combined with community case management of malaria in children under 10 years of age, over 5 months, in south-east Senegal: A cluster-randomised trial.

Ndiaye JLA, Ndiaye Y, Ba MS, Faye B, Ndiaye M, Seck A, Tine R, Thior PM, Atwal S, Beshir K, Sutherland C, Gaye O, Milligan P.
Senegal

BACKGROUND:

Seasonal malaria chemoprevention (SMC) is recommended in the Sahel region of Africa for children under 5 years of age, for up to 4 months of the year. It may be appropriate to include older children, and to provide protection for more than 4 months. We evaluated the effectiveness of SMC using sulfadoxine-pyrimethamine plus amodiaquine given over 5 months to children under 10 years of age in Saraya district in south-east Senegal in 2011.

METHODS AND FINDINGS:
Twenty-four villages, including 2,301 children aged 3-59 months and 2,245 aged 5-9 years, were randomised to receive SMC with community case management (CCM) (SMC villages) or CCM alone (control villages). In all villages, community health workers (CHWs) were trained to treat malaria cases with artemisinin combination therapy after testing with a rapid diagnostic test (RDT). In SMC villages, CHWs administered SMC to children aged 3 months to 9 years once a month for 5 months. The study was conducted from 27 July to 31 December 2011. The primary outcome was malaria (fever or history of fever with a positive RDT). The prevalence of anaemia and parasitaemia was measured in a survey at the end of the transmission season. Molecular markers associated with resistance to SMC drugs were analysed in samples from incident malaria cases and from children with parasitaemia in the survey. SMC was well tolerated with no serious adverse reactions. There were 1,472 RDT-confirmed malaria cases in the control villages and 270 in the SMC villages.
Among children under 5 years of age, the rate difference was 110.8/1,000/month (95% CI 64.7, 156.8; $p < 0.001$) and among children 5-9 years of age, 101.3/1,000/month (95% CI 66.7, 136.0; $p < 0.001$). The mean haemoglobin concentration at the end of the transmission season was higher in SMC than control villages, by 6.5 g/l (95% CI 2.0, 11; $p = 0.007$) among children under 5 years of age, and by 5.2 g/l (95% CI 0.4, 9.9; $p = 0.035$) among children 5-9 years of age. The prevalence of parasitaemia was 18% in children under 5 years of age and 25% in children 5-9 years of age in the control villages, and 5.7% and 5.8%, respectively, in these 2 age groups in the SMC villages, with prevalence differences of 12.5% (95% CI 6.8%, 18.2%; $p < 0.001$) in children under 5 years of age and 19.3% (95% CI 8.3%, 30.2%; $p < 0.001$) in children 5-9 years of age. The pfdhps-540E mutation associated with clinical resistance to sulfadoxine-pyrimethamine was found in 0.8% of samples from malaria cases but not in the final survey. Twelve children died in the control group and 14 in the SMC group, a rate difference of 0.096/1,000 child-months (95% CI 0.99, 1.18; $p = 0.895$). Limitations of this study include that we were not able to obtain blood smears for microscopy for all suspected malaria cases, such that we had to rely on RDTs for confirmation, which may have included false positives.

CONCLUSIONS:
In this study SMC for children under 10 years of age given over 5 months was feasible, well tolerated, and effective in preventing malaria episodes, and reduced the prevalence of parasitaemia and anaemia. **SMC with CCM achieved high coverage and ensured children with malaria were promptly treated with artemether-lumefantrine.**

Malar J. 2018 Nov 3;17(1):405. doi: 10.1186/s12936-018-2541-9. (Open access available)

The dynamic of asymptomatic Plasmodium falciparum infections following mass drug administrations with dihydroarteminisin-piperaquine plus a single low dose of primaquine in Savannakhet Province, Laos.

Pongvongsa T, Phommasone K, Adhikari B, Henriques G, Chotivanich K, Hanboonkunupakarn B, Mukaka M, Peerawaranun P, von Seidlein L, Day NPJ, White NJ, Dondorp AM, Imwong M, Newton PN, Singhasivanon P, Mayxay M, Pukrittayakamee S
Thailand, Laos, UK

BACKGROUND:
The increase in multidrug resistant Plasmodium falciparum infections threatens the malaria elimination goals in countries within the Greater Mekong Sub-region. **A multi-pronged approach assuring access to basic malaria control measures, including insecticide-treated bed nets and early diagnosis and treatment was followed by mass drug administrations (MDA) in southern Savannakhet Province, Laos**. The main objective of this study was to evaluate the effectiveness and safety of mass drug administrations as well as their effects on the dynamic of asymptomatic P. falciparum infections in 4 malaria endemic villages.

METHODS:
Two villages were randomized to early MDA consisting of 3 rounds of a 3-day course of dihydroartemisinin-piperaquine with a single low dose of primaquine. In the other 2 villages MDA was deferred by 1 year. A total of 1036 residents were enrolled in early MDA villages and 883 in control villages (deferred-MDA). Tri-monthly parasitaemia surveys using uPCR were conducted for a year in the 4 villages.

RESULTS:
Eighty-four percent (872/1036) of the residents participated in the MDAs, of whom 90% (781/872) completed 3 rounds of MDA (9 doses). **In intervention villages, the prevalence of asymptomatic P. falciparum infections decreased by 85% after MDA from 4.8% (95% CI 3.4-6.4) at baseline (month 0 or M0) to 0.7% (95% CI 0.3-1.6) at month 12. In control villages there was a decrease of 33% in P. falciparum prevalence between M0: 17.5% (95% CI 15.9-20.3) and M12: 11.6% (95% CI 9.3-14.2).** In bivariate and multivariate analyses P. falciparum infections were significantly reduced with early MDA (adjusted incidence rate ratios (AIRR): 0.08, CI 0.01-0.091) and completion of 3 MDA rounds (AIRR: 0.06; CI 0.01-0.66). A quarter of participants (226/872) reported adverse events of which 99% were mild.

CONCLUSION:
The study found a significant reduction in P. falciparum prevalence and incidence following MDA. MDA was safe, well tolerated, feasible, and achieved high population coverage and adherence. MDAs must be integrated in multi-pronged approaches such as vector control and preventive measures with a focus on specific risk groups such as mobile, migrant population and forest goers for a sustained period to eliminate the remaining parasite reservoirs. Trial registration ClinicalTrials.gov Identifier: NCT01872702.

BMC Med. 2018 Dec 10;16(1):215. doi: 10.1186/s12916-018-1202-8. (Open access available)

A cluster randomised controlled trial of two rounds of mass drug administration in Zanzibar, a malaria pre-elimination setting-high coverage and safety, but no significant impact on transmission.

Morris U, Msellem MI, Mkali H, Islam A, Aydin-Schmidt B, Jovel I, Shija SJ, Khamis M, Ali SM, Hodzic L, Magnusson E, Poirot E, Bennett A, Sachs MC, Tarning J, Mårtensson A, Ali AS, Björkman A.
Sweden, Tanzania, USA, Thailand, UK.

BACKGROUND:
Mass drug administration (MDA) has the potential to interrupt malaria transmission and has been suggested as a tool for malaria elimination in low-endemic settings. This study aimed to determine the effectiveness and safety of two rounds of MDA in Zanzibar, a pre-elimination setting.

METHODS:
A cluster randomised controlled trial was conducted in 16 areas considered as malaria hotspots, with an annual parasite index of > 0.8%. The areas were randomised to eight intervention and eight control clusters. **The intervention included two rounds of MDA with dihydroartemisinin-piperaquine and single low-dose primaquine 4 weeks apart in May-June 2016. Primary and secondary outcomes were cumulative confirmed malaria case incidences 6 months post-MDA and parasite prevalences determined by PCR 3 months post-MDA**. Additional outcomes included intervention coverage, treatment adherence, occurrence of adverse events, and cumulative incidences 3, 12, and 16 months post-MDA.

RESULTS:
Intervention coverage was 91.0% (9959/10944) and 87.7% (9355/10666) in the first and second rounds, respectively; self-reported adherence was 82.0% (881/1136) and 93.7% (985/1196). Adverse events were reported in 11.6% (147/1268) and 3.2% (37/1143) of post-MDA survey respondents after both rounds respectively. No serious adverse event was reported. **No difference in cumulative malaria case incidence was observed between the control and intervention arms 6 months post-MDA (4.2 and 3.9 per 1000 population; p = 0.94). Neither was there a difference in PCR-determined parasite prevalences 3 months post-MDA (1.4% and 1.7%; OR = 1.0, p = 0.94)**, although having received at least the first MDA was associated with reduced odds of malaria infection (aOR = 0.35; p = 0.02). Among confirmed malaria cases at health facilities, 26.0% and 26.3% reported recent travel outside Zanzibar in the intervention and control shehias (aOR ≥ 85; p ≤ 0.001).

CONCLUSIONS:
MDA was implemented with high coverage, adherence, and tolerability. Despite this, no significant impact on transmission was observed. The findings suggest that two rounds of MDA in a single year may not be sufficient for a sustained impact on transmission in a pre-elimination setting, especially when the MDA impact is restricted by imported malaria.

Importantly, this study adds to the limited evidence for the use of MDA in low transmission settings in sub-Saharan Africa.

Lancet. 2019 Apr 13;393(10180):1517-1526. doi: 10.1016/S0140-6736(18)32321-3. Epub 2019 Mar 14. (Open access available)

Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial.

Foy BD, Alout H, Seaman JA, Rao S, Magalhaes T, Wade M, Parikh S, Soma DD, Sagna AB, Fournet F, Slater HC, Bougma R, Drabo F, Diabaté A, Coulidiaty AGV, Rouamba N, Dabiré RK.

BACKGROUND:
Ivermectin is widely used in mass drug administrations for controlling neglected parasitic diseases, and can be lethal to malaria vectors that bite treated humans. Therefore, it could be a new tool to reduce plasmodium transmission. We tested the hypothesis that frequently repeated mass administrations of ivermectin to village residents would reduce clinical malaria episodes in children and would be well tolerated with minimal harms.

METHODS:
We invited villages (clusters) in Burkina Faso to participate in a single-blind (outcomes assessor), parallel-assignment, two-arm, cluster-randomised trial over the 2015 rainy season. Villages were assigned (1:1) by random draw to either the intervention group or the control group. In both groups, all eligible participants who consented to the treatment and were at least 90 cm in height received single oral doses of ivermectin (150-200 μg/kg) and albendazole (400 mg), and those in the intervention group received five further doses of ivermectin alone at 3-week intervals thereafter over the 18-week treatment phase. The primary outcome was cumulative incidence of uncomplicated malaria episodes over 18 weeks (analysed on a cluster intention-to-treat basis) in an active case detection cohort of children aged 5 years or younger living in the study villages. This trial is registered with ClinicalTrials.gov, number NCT02509481.

FINDINGS:
Eight villages agreed to participate, and four were randomly assigned to each group. 2712 participants (1333 [49%] males and 1379 [51%] females; median age 15 years [IQR 6-34]), including 590 children aged 5 years or younger, provided consent and were enrolled between May 22 and July 20, 2015 (except for 77 participants enrolled after these dates because of unavailability before the first mass drug administration, travel into the village during the trial, or birth), with 1447 enrolled into the intervention group and 1265 into the control group. 330 (23%) participants in the intervention group and 233 (18%) in the control group met the exclusion criteria for mass drug administration. Most children in the active case detection cohort were not treated because of height restrictions. 14 (4%) children in the intervention group and 10 (4%) in the control group were lost to follow-up. Cumulative malaria incidence was reduced in the intervention group (648 episodes among 327 children; estimated mean 2·00 episodes per child) compared with the control group (647 episodes

among 263 children; 2·49 episodes per child; risk difference -0·49 [95% CI -0·79 to -0·21], p=0·0009, adjusted for sex and clustering). The risk of adverse events among all participants did not differ between groups (45 events [3%] among 1447 participants in the intervention group vs 24 events [2%] among 1265 in the control group; risk ratio 1·63 [1·01 to 2·67]; risk difference 1·21 [0·04 to 2·38], p=0·060), and no adverse reactions were reported.

INTERPRETATION:
Frequently repeated mass administrations of ivermectin during the malaria transmission season can reduce malaria episodes among children without significantly increasing harms in the populace.

Treatment of uncomplicated malaria

Malar J. 2018 Oct 5;17(1):347. doi: 10.1186/s12936-018-2496-x.

A randomized trial of dihydroartemisinin-piperaquine versus artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Mali.

Dama S, Niangaly H, Djimde M, Sagara I, Guindo CO, Zeguime A, Dara A, Djimde AA, Doumbo OK.
Mali

BACKGROUND:
Artemether-lumefantrine (AL) and artesunate-amodiaquine are first-line treatment for uncomplicated malaria in many endemic countries, including Mali. Dihydroartemisinin-piperaquine (DHA-PQ) is also an alternative first-line artemisinin-based combination therapy, but only few data are available on DHA-PQ efficacy in sub-Saharan Africa. The main aim of this study was to compare clinical efficacy of DHA-PQ versus AL, using the World Health Organization (WHO) 42-day in vivo protocol.

METHODS:
The efficacy of three-dose regimens of DHA-PQ was compared to AL combination in a randomized, comparative open label trial using the WHO 42-day follow-up protocol from 2013 to 2015 in Doneguebougou and Torodo, Mali. The primary endpoint was to access the PCR-corrected Adequate Clinical and Parasitological Responses at day 28.

RESULTS:
A total of 317 uncomplicated malaria patients were enrolled, with 159 in DHA-PQ arm and 158 in AL arm. The parasite positivity rate decreased from 68.4% (95% CI 60.5-75.5) on day 1 to 3.8% (95% CI 1.4-8.1) on day 2 for DHA-PQ and 79.8% (95% CI 72.3-85.7) on day 1 to 9.5% (95% CI 5.4-15.2) on day 2 for AL, (p = 0.04). There was a significant difference in the uncorrected ACPR between DHA-PQ and AL, both at 28-day and 42-day follow-up with 97.4% (95% CI 93.5-99.3) in DHA-PQ vs 84.5% (95% CI 77.8-89.8) in AL (p < 0.001) and 94.2% (95% CI 89.3-97.3) in DHA-PQ vs 73.4% (95% CI 65.7-80.2) in AL, respectively (p < 0.001). After

molecular correction, there was no significant difference in ACPRc between DHA-PQ and AL, both at the 28-day and 42-day follow-up with 99.4% (95% CI 96.5-100) in DHA-PQ versus 98.1% (95% CI 94.5-99.6) in AL (p = 0.3) and 99.3% (95% CI 96.5-100) in DHA-PQ vs 97.4% (95% CI 93.5-99.3) in AL (p = 0.2). There was no significant difference between DHA-PQ and AL in QTc prolongation 12.1% vs 7%, respectively (p = 0.4).

CONCLUSION:
The results showed that dihydroartemisinin-piperaquine and artemether-lumefantrine were clinically efficacious on Plasmodium falciparum parasites in Mali.

Trans R Soc Trop Med Hyg. 2019 Mar 20. pii: trz009. doi: 10.1093/trstmh/trz009. [Epub ahead of print] (Open access available)

Efficacy of artemether-lumefantrine versus dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria among children in Rwanda: an open-label, randomized controlled trial.

Uwimana A, Penkunas MJ, Nisingizwe MP, Warsame M, Umulisa N, Uyizeye D, Musanabaganwa C, Munyaneza T, Ntagwabira E, Hakizimana D, Muvunyi CM, Kayobotsi C, Kabera M, Murindahabi M, Mbituyumuremyi A.
Rwanda

BACKGROUND:
Artemisinin-based combination therapies (ACTs) have proven highly effective in reducing malaria morbidity in sub-Saharan Africa. Artemether-lumefantrine (AL) was introduced in 2005 as a first-line ACT for the treatment of uncomplicated malaria in Rwanda. Monitoring the therapeutic efficacy of ACTs is necessary to ensure effective malaria case management.

METHODS:
A comparative study on the efficacy of **AL and dihydroartemisinin-piperaquine (DHP) was conducted in two sites, Masaka and Ruhuha**, between September 2013 and December 2015. Clinical and parasitological responses were assessed at days 28 and 42.

RESULTS:
A total of 534 children were treated with AL (n=267) or DHP (n=267). After polymerase chain reaction (PCR) adjustment, 98.3% and 98.9% of children in the AL and DHP arms, respectively, achieved an adequate clinical and parasitological response (ACPR) at day 28. At day 42, PCR-adjusted ACPR proportions were 97.3% and 98.4% for AL and DHP, respectively. PCR-adjusted ACPR was 99% for both drugs at days 28 and 42 in Ruhuha. The PCR-adjusted ACPR proportions in Masaka were 97.3% for AL and 98.5% for DHP at day 28 and 95.2% for AL and 97.5% for DHP at day 42.

CONCLUSIONS:
AL remains efficacious in Rwanda 10 y after its adoption. The probability of newinfections occurring among patients in the DHP arm was significantly lower than those in the AL arm.

DHP also demonstrated a greater post-treatment prophylactic effect against new infections compared with AL.

Malar J. 2018 Jul 11;17(1):261. doi: 10.1186/s12936-018-2409-z. (Open access available)

High efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Muheza and Kigoma Districts, Tanzania.

Mandara CI, Kavishe RA, Gesase S, Mghamba J, Ngadaya E, Mmbuji P, Mkude S, Mandike R, Njau R, Mohamed A, Lemnge MM, Warsame M, Ishengoma DS.
Tanzania, WHO, Switzerland

BACKGROUND:
Artemether-lumefantrine (AL) is the recommended first-line artemisinin-based combination therapy (ACT) for the treatment of uncomplicated falciparum malaria in most of the malaria-endemic countries, including Tanzania. Recently, dihydroartemisinin-piperaquine (DP) has been recommended as the alternative anti-malarial to ensure effective case management in Tanzania. **This study assessed the parasite clearance rate and efficacy of AL and DP among patients aged 6 months to 10 years with uncomplicated falciparum malaria in two sites with different malaria transmission intensity**.

METHODS:
This was an open-label, randomized trial that was conducted at two sites of Muheza Designated District Hospital and Ujiji Health Centre in Tanga and Kigoma regions, respectively. Patients meeting inclusion criteria were enrolled, treated with either AL or DP and followed up for 28 (extended to 42) and 42 (63) days for AL and DP, respectively. Parasite clearance time was monitored in the first 72 h post treatment and the clearance rate constant and half-life were calculated using an established parasite clearance estimator. The primary outcome was parasitological cure on days 28 and 42 for AL and DP, respectively, while secondary outcome was extended parasitological cure on days 42 and 63 for AL and DP, respectively.

RESULTS:
Of the 509 children enrolled (192 at Muheza and 317 at Ujiji), there was no early treatment failure and PCR uncorrected cure rates on day 28 in the AL group were 77.2 and 71.2% at Muheza and Ujiji, respectively. In the DP arm, the PCR uncorrected cure rate on day 42 was 73.6% at Muheza and 72.5% at Ujiji. With extended follow-up (to day 42 for AL and 63 for DP) cure rates were lower at Ujiji compared to Muheza (AL: 60.2 and 46.1%, p = 0.063; DP: 57.6 and 40.3% in Muheza and Ujiji, respectively, p = 0.021). The PCR corrected cure rate ranged from 94.6 to 100% for all the treatment groups at both sites. Parasite clearance rate constant was similar in the two groups and at both sites (< 0.28/h); the slope half-life was < 3.0 h and all but only one patient cleared parasites by 72 h.

CONCLUSION:

These findings confirm high efficacy of the first- and the newly recommended alternative ACT for treatments for uncomplicated falciparum malaria in Tanzania. The high parasite clearance rate suggests absence of suspected artemisinin resistance, defined as delayed parasite clearance.

Malar J. 2018 Jul 11;17(1):258. doi: 10.1186/s12936-018-2404-4. (Open access available)

Effectiveness and safety of 3 and 5 day courses of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in an area of emerging artemisinin resistance in Myanmar.

Tun KM, Jeeyapant A, Myint AH, Kyaw ZT, Dhorda M, Mukaka M, Cheah PY, Imwong M, Hlaing T, Kyaw TH, Ashley EA, Dondorp A, White NJ, Day NPJ, Smithuis F.
Myanmar, UK, Thailand,

BACKGROUND:
Artemisinin resistance in Plasmodium falciparum has emerged and spread in Southeast Asia. In areas where resistance is established longer courses of artemisinin-based combination therapy have improved cure rates.

METHODS:
The standard 3-day course of artemether-lumefantrine (AL) was compared with an extended 5-day regimen for the treatment of uncomplicated falciparum malaria in Kayin state in South-East Myanmar, an area of emerging artemisinin resistance. Late parasite clearance dynamics were described by microscopy and quantitative ultra-sensitive PCR. Patients were followed up for 42 days.

RESULTS:
Of 154 patients recruited (105 adults and 49 children < 14 years) 78 were randomized to 3 days and 76 to 5 days AL. Mutations in the P. falciparum kelch13 propeller gene (k13) were found in 46% (70/152) of infections, with F446I the most prevalent propeller mutation (29%; 20/70). Both regimens were well-tolerated. Parasite clearance profiles were biphasic with a slower submicroscopic phase which was similar in k13 wild-type and mutant infections. **The cure rates were 100% (70/70) and 97% (68/70) in the 3- and 5-day arms respectively.** Genotyping of the two recurrences was unsuccessful.

CONCLUSION:
Despite a high prevalence of k13 mutations, the current first-line treatment, AL, was still highly effective in this area of South-East Myanmar. The extended 5 day regimen was very well tolerated, and would be an option to prolong the useful therapeutic life of AL.

Infect Dis Poverty. 2018 Dec 7;7(1):122. doi: 10.1186/s40249-018-0503-7. (Open access available)

Parasite reduction ratio one day after initiation of artemisinin-based combination therapies and its relationship with parasite clearance time in acutely malarious children.

Akano K, Ntadom G, Agomo C, Happi CT, Folarin OA, Gbotosho GO, Mokuolu O, Finomo F, Ebenebe JC, Jiya N, Ambe J, Wammanda R, Emechebe G, Basorun OK, Wewe OA, Amoo S, Ezeigwe N, Oguche S, Fatunmbi B, Sowunmi A.
Nigeria

BACKGROUND:
In acute falciparum malaria, asexual parasite reduction ratio two days post-treatment initiation (PRRD2) ≥ 10 000 per cycle has been used as a measure of the rapid clearance of parasitaemia and efficacy of artemisinin derivatives. However, there is little evaluation of alternative measures; for example, **parasite reduction ratio one day after treatment initiation (PRRD1) and its relationship with parasite clearance time (PCT) or PRRD2. This study evaluated the use of PRRD1 as a measure of responsiveness to antimalarial drugs.**

METHODS:
In acutely malarious children treated with artesunate-amodiaquine (AA), artemether-lumefantrine (AL) or dihydroartemisinin-piperaquine (DHP), the relationships between PRRD1 or PRRD2 and PCT, and between PRRD1 and PRRD2 were evaluated using linear regression. Agreement between estimates of PCT using PRRD1 and PRRD2 linear regression equations was evaluated using the Bland-Altman analysis. Predictors of PRRD1 > 5000 per half cycle and PRRD2 ≥ 10 000 per cycle were evaluated using stepwise multiple logistic regression models. Using the linear regression equation of the relationship between PRRD1 and PCT previously generated in half of the DHP-treated children during the early study phase, PCT estimates were compared in a prospective blinded manner with PCTs determined by microscopy during the later study phase in the remaining half.

RESULTS:
In 919 malarious children, PRRD1 was significantly higher in DHP- and AA-treated compared with AL-treated children (P < 0.0001). PRRD1 or PRRD2 values correlated significantly negatively with PCT values (P < 0.0001 for each) and significantly positively with each other (P < 0.0001). PCT estimates from linear regression equations for PRRD1 and PRRD2 showed insignificant bias on the Bland-Altman plot (P = 0.7) indicating the estimates can be used interchangeably. At presentation, age > 15 months, parasitaemia > 10 000/µl and DHP treatment independently predicted PRRD1 > 5000 per half cycle, while age > 30 months, haematocrit ≥31%, body temperature > 37.4 °C, parasitaemia > 100 000/µl, PRRD1 value > 1000 and no gametocytaemia independently predicted PRRD2 ≥ 10 000 per cycle. Using the linear regression equation generated during the early phase in 166 DHP-treated children, PCT estimates and PCTs determined by microscopy in the 155 children in the later phase were similar in the same patients.

CONCLUSIONS:
PRRD1 and estimates of PCT using PRRD1 linear regression equation of PRRD1 and PCT can be used in therapeutic efficacy studies.

MC Infect Dis. 2019 Mar 12;19(1):250. doi: 10.1186/s12879-019-3862-1. (Open access available)

The tolerability of single low dose primaquine in glucose-6-phosphate deficient and normal falciparum-infected Cambodians.

Dysoley L, Kim S, Lopes S, Khim N, Bjorges S, Top S, Huch C, Rekol H, Westercamp N, Fukuda MM, Hwang J, Roca-Feltrer A, Mukaka M, Menard D, Taylor WR.

Abstract
BACKGROUND:
The WHO recommends single low-dose primaquine (SLDPQ, 0.25 mg/kg body weight) in falciparum-infected patients to block malaria transmission and contribute to eliminating multidrug resistant Plasmodium falciparum from the Greater Mekong Sub region (GMS). However, the anxiety regarding PQ-induced acute haemolytic anaemia in glucose-6-phosphate dehydrogenase deficiency (G6PDd) has hindered its use. Therefore, we assessed the tolerability of SLDPQ in Cambodia to inform national policy.

METHODS:
This open randomised trial of dihydroartemisinin-piperaquine (DHAPP) + SLDPQ vs. DHAPP alone recruited Cambodians aged ≥1 year with acute uncomplicated P. falciparum. Randomisation was 4:1 DHAPP+SLDPQ: DHAPP for G6PDd patients and 1:1 for G6PDn patients, according to the results of the qualitative fluorescent spot test. Definitive G6PD status was determined by genotyping. Day (D) 7 haemoglobin (Hb) concentration was the primary outcome measure.

RESULTS:
One hundred nine patients (88 males, 21 females), aged 4-76 years (median 23) were enrolled; 12 were G6PDd Viangchan (9 hemizygous males, 3 heterozygous females). **Mean nadir Hb occurred on D7 [11.6 (range 6.4 — 15.6) g/dL] and was significantly lower (p = 0.040) in G6PDd (n = 9) vs. G6PDn (n = 46) DHAPP+SLDPQ recipients: 10.9 vs. 12.05 g/dL, Δ = -1.15 (95% CI: -2.24 — -0.05) g/dL.** Three G6PDn patients had D7 Hb concentrations < 8 g/dL; D7-D0 Hbs were 6.4 — 6.9, 7.4 — 7.4, and 7.5 — 8.2 g/dL. For all patients, mean (range) D7-D0 Hb decline was -1.45 (-4.8 — 2.4) g/dL, associated significantly with higher D0 Hb, higher D0 parasitaemia, and receiving DHAPP; G6PDd was not a factor. No patient required a blood transfusion.

CONCLUSIONS:
DHAPP+SLDPQ was associated with modest Hb declines in G6PD Viangchan, a moderately severe variant. Our data augment growing evidence that SLDPQ in SE Asia is well tolerated and appears safe in G6PDd patients. Cambodia is now deploying SLDPQ and this should encourage other GMS countries to follow suit.

Cochrane Database Syst Rev. 2019 Jan 8;1:CD006404. doi: 10.1002/14651858.CD006404.pub3. (Open access available)

Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria.

Pryce J, Hine P.
UK

BACKGROUND:
The World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) to treat uncomplicated Plasmodium falciparum (P 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 Search Portal, and the International Standard Randomized Controlled Trial Number (ISRCTN) registry for ongoing or recently completed trials. The date of the last search was 8 May 2018.

SELECTION CRITERIA:
Efficacy analysis: randomized controlled trials (RCTs) of pyronaridine-artesunate for treating uncomplicated P falciparum malaria.Safety analysis: RCTs of pyronaridine-artesunate or pyronaridine for treating P falciparum or P vivax malaria.

DATA COLLECTION AND ANALYSIS:
For this update, two review authors independently re-extracted all data and assessed certainty of 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 studies. Seven studies were co-funded by Shin Poong Pharmaceuticals which manufactures the drug. Three studies were funded by government agencies.For efficacy analysis we identified five RCTs with 5711 participants. This included 4465 participants from 13 sites in Africa, and 1246 participants from five sites in Asia. It included 541 children aged less than five years.For polymerase chain reaction (PCR)-adjusted failures at day 28, pyronaridine-artesunate may have fewer failures compared to artemether-lumefantrine (RR 0.59, 95% confidence interval (CI) 0.26 to 1.31; 4 RCTs, 3068 participants, low-certainty evidence), artesunate-amodiaquine (RR 0.55, 95% CI 0.11 to 2.77; 1 RCT, 1245

participants, low-certainty evidence), and mefloquine plus artesunate (RR 0.37, 95% CI 0.13 to 1.05; 1 RCT, 1117 participants, low-certainty evidence).For unadjusted failures at day 28, pyronaridine-artesunate may have fewer failures compared to artemether-lumefantrine (RR 0.27, 95% CI 0.13 to 0.58; 4 RCTs, 3149 participants, low-certainty evidence), and probably has fewer failures compared to artesunate-amodiaquine (RR 0.49, 95% CI 0.30 to 0.81; 1 RCT, 1257 participants, moderate-certainty evidence) and mefloquine plus artesunate (RR 0.36, 95% CI 0.17 to 0.78; 1 RCT, 1120 participants, moderate-certainty evidence).For PCR-adjusted failures at day 42, pyronaridine-artesunate may make little or no difference compared to artemether-lumefantrine (RR 0.86, 95% CI 0.49 to 1.51; 4 RCTs, 2575 participants, low-certainty evidence) and artesunate-amodiaquine (RR 0.98, 95% CI 0.20 to 4.83; 1 RCT, 1091 participants, low-certainty evidence), but may have higher failures than mefloquine plus artesunate (RR 1.80, 95% CI 0.90 to 3.57; 1 RCT, 1037 participants, low-certainty evidence). Overall, pyronaridine-artesunate had a PCR-adjusted treatment failure rate of less than 5%.For unadjusted failures at day 42, pyronaridine-artesunate may have fewer failures compared to artemether-lumefantrine (RR 0.61, 95% CI 0.46 to 0.82; 4 RCTs, 3080 participants, low-certainty evidence), may make little or no difference compared to mefloquine plus artesunate (RR 0.84, 95% CI 0.54 to 1.31; 1 RCT, 1059 participants, low-certainty evidence), and probably makes little or no difference compared to artesunate-amodiaquine (RR 0.98, 95% CI 0.78 to 1.23; 1 RCT, 1235 participants, moderate-certainty evidence).For the safety analysis of severe adverse events and liver function, we identified eight RCTs with 6614 participants comparing pyronaridine-artesunate to other antimalarials, four of which were not in the previous version of this review. A further two RCTs, comparing pyronaridine alone to other treatments, contributed to the synthesis of all adverse events.**Raised alanine aminotransferase (ALT) greater than five times the upper limit of normal (> 5 x ULN) is more frequent with pyronaridine-artesunate compared to other antimalarials (RR 3.34, 95% CI 1.63 to 6.84; 8 RCTS, 6581 participants, high-certainty evidence).** There is probably little or no difference for raised bilirubin > 2.5 x ULN between pyronaridine-artesunate and other antimalarials (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, meeting criteria for moderate drug-induced liver injury. 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.

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 raised ALT > 5 x ULN. This meets criteria for mild drug-induced liver injury. On one instance this was linked to raised bilirubin, indicating moderate drug-induced liver injury. No episodes of severe drug-induced liver injury were reported. The findings of this review cannot fully inform a risk-benefit assessment for an unselected population. Readers should remain aware of this uncertainty when considering use of pyronaridine-artesunate in patients with known or suspected pre-existing liver dysfunction, and when co-administering with other medications which may cause liver dysfunction.

Treatment of severe malaria

Cochrane Database Syst Rev. 2019 Jun 18;6:CD010678. doi: 10.1002/14651858.CD010678.pub3. (Open Access available)

Artemether for severe malaria.

Esu EB, Effa EE, Opie ON, Meremikwu MM.
Nigeria.

BACKGROUND:
In 2011 the World Health Organization (WHO) recommended parenteral artesunate in preference to quinine as first-line treatment for people with severe malaria. Prior to this recommendation many countries, particularly in Africa, had begun to use artemether, an alternative artemisinin derivative. This Cochrane Review evaluates intramuscular artemether compared with both quinine and artesunate.
OBJECTIVES:
To assess the efficacy and safety of intramuscular artemether versus any other parenteral medication in the treatment of severe malaria in adults and children.
SEARCH METHODS:
We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (the Cochrane Library), MEDLINE, Embase, and LILACS, ISI Web of Science, conference proceedings, and reference lists of articles. We also searched the WHO International Clinical Trial Registry Platform, ClinicalTrials.gov, and the metaRegister of Controlled Trials (mRCT) for ongoing trials up to 7 September 2018. We checked the reference lists of all studies identified by the search. We examined references listed in review articles and previously compiled bibliographies to look for eligible studies.
SELECTION CRITERIA:
Randomized controlled trials (RCTs) comparing intramuscular artemether with intravenous/intramuscular quinine or artesunate for treating severe malaria.
DATA COLLECTION AND ANALYSIS:
The primary outcome was all-cause death. Two review authors independently screened each article by title and abstract, and examined potentially relevant studies for inclusion using an eligibility form. Two review authors independently extracted data and assessed risk of bias of included studies. We summarized dichotomous outcomes using risk ratios (RRs) and continuous outcomes using mean differences (MDs), and have presented both measures with 95% confidence intervals (CIs). Where appropriate, we combined data in meta-analyses and used the GRADE approach to summarize the certainty of the evidence.
MAIN RESULTS:
We included 19 RCTs, enrolling 2874 adults and children with severe malaria, carried out in Africa (12 trials) and in Asia (7 trials). Artemether versus quinine. **For children, there is probably little or no difference in the risk of death between intramuscular artemether and quinine (RR 0.97, 95% CI 0.77 to 1.21; 13 trials, 1659 participants**, moderate-certainty evidence). Coma resolution time may be about five hours shorter with artemether (MD -5.45, 95% CI -7.90 to -3.00; six trials, 358 participants, low-certainty evidence). Artemether may make little difference to neurological sequelae (RR 0.84, 95% CI 0.66 to 1.07; seven trials, 968 participants, low-certainty evidence). **Compared to quinine, artemether probably shortens the parasite clearance time by about nine hours (MD -9.03, 95% CI -**

11.43 to -6.63; seven trials, 420 participants, moderate-certainty evidence), and may shorten the fever clearance time by about three hours (MD -3.73, 95% CI -6.55 to -0.92; eight trials, 457 participants, low-certainty evidence). Artemether versus artesunate. **Artemether and artesunate have not been directly compared in randomized trials in children**. **For adults, mortality is probably higher with intramuscular artemether** (RR 1.80, 95% CI 1.09 to 2.97; two trials, 494 participants, moderate-certainty evidence).
AUTHORS' CONCLUSIONS:
Artemether appears to be more effective than quinine in children and adults. Artemether compared to artesunate has not been extensively studied, but in adults it appears inferior. These findings are consistent with the WHO recommendations that artesunate is the drug of choice, but artemether is acceptable when artesunate is not available.

Malnutrition

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

Indian Pediatr. 2019 Apr 15;56(4):287-293.

Indigenously Prepared Ready-to-use Therapeutic Food (RUTF) in Children with Severe Acute Malnutrition.

Jadhav AR, Karnik P, Fernandes L, Fernandes S, Shah N, Manglani M.
India

OBJECTIVE:
To compare efficacy of indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy) with Standard Nutrition Therapy in children with Severe acute malnutrition.

DESIGN:
Two facility-based and two community-based models: (i) Open prospective randomized controlled trial comparing Indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy) with Standard Nutrition Therapy; (ii) Only Indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy); (iii) Doorstep Child Care Centre; and (iv) Community-based Management of Acute Malnutrition.

SETTING:
(i) Urban Health Center, Dharavi, Mumbai; (ii) Two day care centers of Non-governmental Organization SNEHA - Mumbai; (iii) Urban slums, M East and L Ward, Mumbai.

PARTICIPANTS:
1105 children aged 6-60 months in community or hospital inpatient/ outpatient department diagnosed as Severe Acute Malnutrition by WHO definition.

INTERVENTION:

All subjects received either Indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy) or Standard Nutrition Therapy (protein calorie rich diet) for eight weeks and followed up for next four months.

MAIN OUTCOME MEASURES:
Mean rate of weight gain (g/kg/day), target weight, change in nutritional status.

RESULTS:
Rate of weight gain was higher (P<0.05) at 2 weeks on indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy) (5.63 g/kg/day) as compared to Standard Nutrition Therapy (3.43 g/kg/day). 61.2% subjects achieved target weight compared to 47.7% controls. At 8 weeks, 82.8% subjects recovered from Severe Acute Malnutrition compared to 19.3% controls (P<0.005). The results obtained in community were comparable to facility-based indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy). The morbidity was less in study group at follow-up.

CONCLUSIONS:
Indigenous Ready-to-use Therapeutic Food (Medical Nutrition Therapy) appeared to be superior to Standard Nutrition Therapy in promoting weight gain in children with Severe Acute Malnutrition.

Nutrients. 2018 Jul 16;10(7). pii: E909. doi: 10.3390/nu10070909. (Open access available)

Effectiveness of a Locally Produced, Fish-Based Food Product on Weight Gain among Cambodian Children in the Treatment of Acute Malnutrition: A Randomized Controlled Trial.

Sigh S, Roos N, Chamnan C, Laillou A, Prak S, Wieringa FT.
Denmark, Cambodia, France

Abstract
Cambodia continues to have a high prevalence of acute malnutrition. Low acceptability has been found for standard ready-to-use-therapeutic-food (RUTF) products. Therefore, **NumTrey, a locally-produced fish-based RUTF**, was developed. The objective was to evaluate the **effectiveness of NumTrey compared to an imported milk-based RUTF for weight gain among children aged 6⁻59 months in the home-treatment for acute malnutrition**. Effectiveness was tested in a single-blinded randomized controlled trial with **weight gain as the primary outcome**. Anthropometry was assessed at baseline and bi-weekly follow-ups until endline at Week 8. In total, **121 patients were randomized into BP-100 (*n* = 61) or NumTrey (*n* = 60)**. **There was no statistical difference in mean weight gain between the groups (1.06 g/kg/day; 95% CI (0.72, 1.41) and 1.08 g/kg/day; 95% CI (0.75, 1.41) for BP-100™ and NumTrey, respectively)**. In addition, no statistically significant differences in secondary outcomes were found. Although the ability to draw conclusions was limited by lower weight gain than the desired 4 g/kg/day in both groups, no superiority was found for eitherRUTF. A locally produced RUTF is highly relevant to improve nutrition

interventions in Cambodia. **A locally produced fish-based RUTF is a relevant alternative to imported milk-based RUTF for the treatment of SAM in Cambodia**.

PLoS One. 2018 Aug 10;13(8):e0201686. doi: 10.1371/journal.pone.0201686. eCollection 2018. (Open access available)

Amino-acid-enriched cereals ready-to-use therapeutic foods (RUTF) are as effective as milk-based RUTF in recovering essential amino acid during the treatment of severe acute malnutrition in children: An individually randomized control trial in Malawi.

Sato W, Furuta C, Matsunaga K, Bahwere P, Collins S, Sadler K, Akomo P, Banda C, Maganga E, Kathumba S, Murakami H.
Japan, UK, Belgium, Republic of Ireland, Malawi

BACKGROUND:
Ready-to-use therapeutic food (RUTF) is used to treat children suffering from severe acute malnutrition (SAM). Standard RUTF uses milk as the primary protein source, which makes the product expensive, and given the high worldwide SAM burden, having a less expensive effective alternative is a public health priority.

OBJECTIVE:
The objective of this study was to evaluate whether newly developed amino acid-enriched milk-free RUTF (FSMS-RUTF) or amino acid-enriched low-milk RUTF (MSMS-RUTF) treatment could replenish plasma amino acids to levels comparable to those following standard peanut-milk RUTF (PM-RUTF) treatment and to improve understanding of the effects of treatment on anthropometric measurements. A secondary analysis was performed to test the noninferiority hypothesis of plasma essential amino acid (EAA) levels.

METHODS:
Plasma EAA levels were measured in a nonblinded, 3-arm, parallel-group simple randomized controlled trial conducted in Malawi to examine the efficacy of FSMS-RUTF, MSMS-RUTF and PM-RUTF in the treatment of SAM in 2 groups of children aged 6-23 and 24-59 months (mo). Sample size calculations were performed based on the previous our study. A noninferiority margin was set at -25% of the PM-RUTF arm at discharge.

RESULTS:
The relative values of the differences (95% CI) in plasma EAA levels between PM-RUTF treatment and FSMS-RUTF and MSMS-RUTF treatments at discharge were -7.9% (-18.6, 2.8) and 9.8% (0.2, 19.5), respectively, in children aged 6-23 mo, while in those aged 24-59 mo, the difference values were 17.8% (1.6, 34.1) and 13.6% (-2.8, 29.9), respectively.

CONCLUSION:
At discharge, the plasma EAA concentrations in 6-59-mo-old SAM children treated with FSMS-RUTF and MSMS-RUTF were not less than those of children treated with PM-RUTF. These

findings indicate that treatment with either of the 3 RUTFs was associated with adequate protein synthesis and that all the formulations provided sufficient functional metabolites of plasma amino acids to support nutritional recovery from SAM.

BMC Public Health. 2019 Jan 17;19(1):84. doi: 10.1186/s12889-018-6382-9. (Open access available)

Evaluation of the cost-effectiveness of the treatment of uncomplicated severe acute malnutrition by lady health workers as compared to an outpatient therapeutic feeding programme in Sindh Province, Pakistan.

Rogers E, Guerrero S, Kumar D, Soofi S, Fazal S, Martínez K, Morán JLA, Puett C.

UK, USA, Pakistan

BACKGROUND:
Due to the limited evidence of the cost-effectiveness of Community Health Workers (CHW) delivering treatment for severe acute malnutrition (SAM), there is a need to better understand the costs incurred by both implementing institutions and beneficiary households. **This study assessed the costs and cost-effectiveness of treatment for cases of SAM without complications delivered by government-employed Lady Health Workers (LHWs) and complemented with non-governmental organisation (NGO) delivered outpatient facility-based care compared with NGO delivered outpatient facility-based care only** alongside a two-arm randomised controlled trial conducted in Sindh Province, Pakistan.

METHODS:
An activity-based cost model was used, employing a societal perspective to include costs incurred by beneficiaries and the wider community. Costs were estimated through accounting records, interviews and informal group discussions. Cost-effectiveness was assessed for each arm relative to no intervention, and incrementally between the two interventions, providing information on both absolute and relative costs and effects.

RESULTS:
The cost per child recovered in outpatient facility-based care was similar to LHW-delivered care, at 363 USD and 382 USD respectively. An additional 146 USD was spent per additional child recovered by outpatient facilities compared to LHWs. Results of sensitivity analyses indicated considerable uncertainty in which strategy was most cost-effective due to small differences in cost and recovery rates between arms. The cost to the beneficiary household of outpatient facility-based care was double that of LHW-delivered care.

CONCLUSIONS:
Outpatient facility-based care was found to be slightly more cost-effective compared to LHW-delivered care, despite the potential for cost-effectiveness of CHWs managing SAM being demonstrated in other settings. **The similarity of cost-effectiveness outcomes between the two models resulted in uncertainty as to which strategy was the most cost-effective.** Similarity of costs and effectiveness between models suggests that whether it is

appropriate to engage LHWs in substituting or complementing outpatient facilities may depend on population needs, including coverage and accessibility of existing services, rather than be purely a consideration of cost. Future research should assess the cost-effectiveness of LHW-delivered care when delivered solely by the government.

Nutrients. 2018 Aug 24;10(9). pii: E1158. doi: 10.3390/nu10091158. (Open access available)

Biomarkers of Systemic Inflammation and Growth in Early Infancy are Associated with Stunting in Young Tanzanian Children.

Syed S, Manji KP, McDonald CM, Kisenge R, Aboud S, Sudfeld C, Locks L, Liu E, Fawzi WW, Duggan CP.
USA, Tanzania

Abstract
Stunting can afflict up to one-third of children in resource-constrained countries. We hypothesized that low-grade systemic inflammation (defined as elevations in serum C-reactive protein or alpha-1-acid glycoprotein) in infancy suppresses the growth hormone⁻insulin-like growth factor (IGF) axis and is associated with subsequent stunting. Blood samples of 590 children from periurban Dar es Salaam, Tanzania, were obtained at 6 weeks and 6 months of age as part of a randomized controlled trial. Primary outcomes were stunting, underweight, and wasting (defined as length-for-age, weight-for-age and weight-for-length *z*-scores < -2) between randomization and endline (18 months after randomization). Cox proportional hazards models were constructed to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of time to first stunting, underweight, and wasting as outcomes, with measures of systemic inflammation, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) as exposures, adjusting for numerous demographic and clinical variables. The incidences of subsequent stunting, underweight, and wasting were 26%, 20%, and 18%, respectively. In multivariate analyses, systemic inflammation at 6 weeks of age was significantly associated with stunting (HR: 2.14, 95% CI: 1.23, 3.72; $p = 0.002$). Children with higher levels of IGF-1 at 6 weeks were less likely to become stunted (HR: 0.58, 95% CI: 0.37, 0.93; p for trend = 0.019); a similar trend was noted in children with higher levels of IGF-1 at 6 months of age (HR: 0.50, 95% CI: 0.22, 1.12; p for trend = 0.07). Systemic inflammation occurs as early as 6 weeks of age and is associated with the risk of future stunting among Tanzanian children.

J Pediatr Gastroenterol Nutr. 2019 May 6. doi: 10.1097/MPG.0000000000002381.

Correlates of gut function in children hospitalized for severe acute malnutrition, a cross-sectional study in Uganda.

Lanyero B[1,2], Grenov B[1], Barungi NN[1,3], Namusoke H[2], Michaelsen KF[1], Mupere E[3], Mølgaard C[1], Jiang P[4], Frøkiær H[4], Wiese M[5], Muhammed MK[5], Pesu H[1], Nielsen DS[5], Friis H[1], Rytter MJ[1], Christensen VB
Denmark, Uganda

OBJECTIVE:
Children with severe acute malnutrition (SAM) may have impaired intestinal function which can result in malabsorption, diarrhoea and poor growth. This study evaluated the gut function of children with SAM using fecal and blood biomarkers and assessed their correlates.
METHODS:
A cross-sectional study, nested in a randomized trial (http://www.isrctn.com, ISRCTN 16454889), was conducted at Mulago hospital, Uganda among subgroups of 400 children with complicated SAM and 30 community controls. Gut function was evaluated by five biomarkers: plasma citrulline, fecal myeloperoxidase and fecal neopterin, bacterially derived 16S rRNA gene and internal transcribed Spacer region (ITS) specific for Candida in blood.
RESULTS:
Compared to controls, children with SAM had lower median plasma citrulline (5.14 vs. 27.4 μmol/l, p<0.001), higher median fecal myeloperoxidase (18083 vs 7482 ng/ml, p=0.001) and fecal neopterin (541 vs 210 nmol/l, p<0.001). A higher blood concentration of 16S rRNA gene copy numbers was observed among children with SAM (95 vs 28 copies/μl, p=0.05), while there was no difference in the blood concentration of Candida specific ITS fragment.Among those with SAM, plasma citrulline was lower in children with oedema, diarrhoea, dermatosis, and plasma C-reactive protein (CRP) >10 mg/l. Fecal neopterin was positively correlated with symptoms of fever and cough whereas it was negatively correlated with MUAC, WHZ, oedema and dermatosis CONCLUSION:: Children with complicated SAM seem to have impaired gut function characterized by reduced enterocyte mass, intestinal inflammation, and increased bacterial translocation.

Maternal health

(see also Malaria)

Antenatal care

PLoS Med. 2019 Mar 29;16(3):e1002768. doi: 10.1371/journal.pmed.1002768. eCollection 2019 Mar. (Open access available)

Community health workers to improve uptake of maternal healthcare services: A cluster-randomized pragmatic trial in Dar es Salaam, Tanzania.

Geldsetzer P, Mboggo E, Larson E, Lema IA, Magesa L, Machumi L, Ulenga N, Sando D, Mwanyika-Sando M, Spiegelman D, Mungure E, Li N, Siril H, Mujinja P, Naburi H, Chalamilla G, Kilewo C, Ekström AM, Foster D, Fawzi W, Bärnighausen T.
Tanzania

BACKGROUND:
Home delivery and late and infrequent attendance at antenatal care (ANC) are responsible for substantial avoidable maternal and pediatric morbidity and mortality in sub-

Saharan Africa. This cluster-randomized trial aimed to determine the impact of a community health worker (CHW) intervention on the proportion of women who (i) visit ANC fewer than 4 times during their pregnancy and (ii) deliver at home.

METHODS AND FINDINGS:
As part of a 2-by-2 factorial design, we conducted a cluster-randomized trialof a home-based CHW intervention in 2 of 3 districts of Dar es Salaam from 18 June 2012 to 15 January 2014. Thirty-six wards (geographical areas) in the 2 districts were randomized to the CHW intervention, and 24 wards to the standard of care. In the standard-of-care arm, CHWs visited women enrolled in prevention of mother-to-child HIV transmission (PMTCT) care and provided information and counseling. **The intervention arm included additional CHW supervision and the following additional CHW tasks, which were targeted at all pregnant women regardless of HIV status: (i) conducting home visits to identify pregnant women and refer them to ANC, (ii) counseling pregnant women on maternal health, and (iii) providing home visits to women who missed an ANC or PMTCT appointment**. The primary endpoints of this trial were the proportion of pregnant women (i) not making at least 4 ANC visits and (ii) delivering at home. The outcomes were assessed through a population-based household survey at the end of the trial period. We did not collect data on adverse events. A random sample of 2,329 pregnant women and new mothers living in the study area were interviewed during home visits. At the time of the survey, the mean age of participants was 27.3 years, and 34.5% (804/2,329) were pregnant. **The proportion of women who reported having attended fewer than 4 ANC visits did not differ significantly between the intervention and standard-of-care arms (59.1% versus 60.7%, respectively; risk ratio [RR]: 0.97; 95% CI: 0.82-1.15; p = 0.754)**. Similarly, the proportion reporting that they had attended ANC in the first trimester did not differ significantly between study arms. **However, women in intervention wards were significantly less likely to report having delivered at home (3.9% versus 7.3%; RR: 0.54; 95% CI: 0.30-0.95; p = 0.034).** Mixed-methods analyses of additional data collected as part of this trial suggest that an important reason for the lack of effect on ANC outcomes was the perceived high economicburden and inconvenience of attending ANC. The main limitations of this trial were that (i) the outcomes were ascertained through self-report, (ii) the study was stopped 4 months early due to a change in the standard of care in the other trial that was part of the 2-by-2 factorial design, and (iii) the sample size of the household survey was not prespecified.

CONCLUSIONS:
A home-based CHW intervention in urban Tanzania significantly reduced the proportion of women who reported having delivered at home, in an area that already has very high uptake of facility-based delivery. The intervention did not affect self-reported ANC attendance. Policy makers should consider piloting, evaluating, and scaling interventions to lessen the economic burden and inconvenience of ANC.

Matern Child Health J. 2019 May;23(5):633-640. doi: 10.1007/s10995-018-2677-9.

An Incentive-Based and Community Health Worker Package Intervention to Improve Early Utilization of Antenatal Care: Evidence from a Pilot Randomised Controlled Trial.

Rossouw L, Burger RP, Burger R.
South Africa

Abstract
One of the factors linked to South Africa's relatively high maternal mortality ratio is late utilization of antenatal care (ANC). Early utilization is especially important in South Africa due to the high HIV prevalence amongst pregnant women. **This study examined the impact of a package intervention, consisting of an incentive called the Thula Baba Box (TBB) and a community health worker (CHW) programme, on early utilization of ANC.** Methods A pilot randomised controlled trial consisting of 72 women aged 18 and older was conducted in an urban area in South Africa to evaluate the impact of the package intervention. **Women were recruited and randomised into either intervention (n = 39) or control group (n = 33).** The intervention group received both the TBB and monthly CHW visits, while the control group followed standard clinical practice. Both groups were interviewed at recruitment and once again after giving birth. **The outcomes measured are the timing of first ANC visit and whether they attended more than four times**. It is anticipated that the box will also have a beneficial impact on infant health outcomes, but these fall out of the scope of this study. Results Women in the intervention groups sought care on average 1.35 months earlier than the control group. They were also significantly more likely to attend at least four antenatal clinic visits. Conclusions for practice Given the South African context and the importance of early care-seeking behaviour to improve health outcomes of HIV-positive pregnant women, the intervention can help to improve maternal and neonatal health outcomes. Further research is needed to investigate the impact of the two interventions separately, and to see if these findings hold in other communities.

Lancet Glob Health. 2019 Jan;7(1):e148-e159. doi: 10.1016/S2214-109X(18)30441-8. (Open access available)

Effect of population-based antenatal screening and treatment of genitourinary tract infections on birth outcomes in Sylhet, Bangladesh (MIST): a cluster-randomised clinical trial.

Lee AC, Mullany LC, Quaiyum M, Mitra DK, Labrique A, Christian P, Ahmed P, Uddin J, Rafiqullah I, DasGupta S, Rahman M, Koumans EH, Ahmed S, Saha SK, Baqui AH; Projahnmo Study Group in Bangladesh.
USA, Bangladesh,

BACKGROUND:
One-third of preterm births are attributed to pregnancy infections. We implemented a community-based intervention to screen and treat maternal genitourinary tract infections, with the aim of reducing the incidence of preterm birth.

METHODS:

We did an unblinded cluster-randomised controlled trial in two subdistricts of Sylhet, Bangladesh. Clusters were defined as the contiguous area served by a single community health worker, and **each cluster comprised several contiguous villages, contained roughly 4000 people, and had about 120 births per year. Eligible participants within clusters were all ever-married women and girls of reproductive age (ie, aged 15-49 years) who became pregnant during the study period.** Clusters were randomly assigned (1:1) to the intervention or control groups via a restricted randomisation procedure. In both groups, community health workers made home visits to identify pregnant women and girls and provide antenatal and postnatal care. **Between 13 and 19 weeks' gestation, participants in the intervention group received home-based screening for abnormal vaginal flora and urinary tract infections**. A random 10% of the control group also received the intervention to examine the similarity of infection prevalence between groups. **If present, abnormal vaginal flora (ie, Nugent score ≥4 was treated with oral clindamycin (300 mg twice daily for 5 days) and urinary tract infections with cefixime (400 mg once daily for 3 days) or oral nitrofurantoin (100 mg twice daily for 7 days).** Both infections were retreated if persistent. The primary outcome was the incidence of preterm livebirths before 37 weeks' gestation among all livebirths. This trial is registered with ClinicalTrials.gov, number NCT01572532. The trial is closed to new participants, with follow-up completed.

FINDINGS:
Between Jan 2, 2012, and July 28, 2015, 9712 pregnancies were enrolled (4840 in the intervention group, 4391 in the control group, and 481 in the control subsample). 3818 livebirths in the intervention group and 3557 livebirths in the control group were included in the primary analysis. **In the intervention group, the prevalence of abnormal vaginal flora was 16·3% (95% CI 15·1-17·6) and that of urinary tract infection was 8·6% (7·7-9·5). The effective coverage of successful treatment in the intervention group was 58% in participants with abnormal vaginal flora (ie, abnormal vaginal flora resolved in 361 [58%] of the 622 participants who initially tested positive), and 71% in those with urinary tract infections (ie, resolution in 224 [71%] of the 317 participants who initially tested positive). Overall, the incidence of preterm livebirths before 37 weeks' gestation did not differ significantly between the intervention and control groups (21·8% vs 20·6%; relative risk 1·07 [95% CI 0·91-1·24]).**
INTERPRETATION:
A population-based antenatal screening and treatment programme for genitourinary tract infections did not reduce the incidence of preterm birth in Bangladesh.

Open Forum Infect Dis. 2019 Jan 14;6(2):ofz011. doi: 10.1093/ofid/ofz011. eCollection 2019 Feb. (Open access available)

Effect of Diarrheal Illness During Pregnancy on Adverse Birth Outcomes in Nepal.

Newman KL, Gustafson K, Englund JA, Magaret A, Khatry S, LeClerq SC, Tielsch JM, Katz J, Chu HY.

Nepal

BACKGROUND:
Adverse birth outcomes, including low birthweight, small for gestational age (SGA), and preterm birth, contribute to 60%-80% of infant mortality worldwide. Little published data exist on the association between diarrhea during pregnancy and adverse birth outcomes.

METHODS:
Data were used from 2 community-based, prospective randomized trials of maternal influenza immunization during pregnancy conducted in rural Nepal from 2011 to 2014. Diarrheal illnesses were identified through longitudinal household-based weekly symptom surveillance. Diarrhea episodes were defined as at least 3 watery bowel movements per day for 1 or more days with 7 diarrhea-free days between episodes. The Poisson and log-binomial regression were performed to evaluate baseline characteristics and association between diarrhea during pregnancy and adverse birth outcomes.

RESULTS:
A total of 527 of 3693 women in the study (14.3%) experienced diarrhea during pregnancy. Women with diarrhea had a median of 1 episode of diarrhea (interquartile range [IQR], 1-2 episodes) and 2 cumulative days of diarrhea (IQR, 1-3 days). Of women with diarrhea, 85 (16.1%) sought medical care. **In crude and adjusted analyses, women with diarrhea during pregnancy were more likely to have SGA infants (42.6% vs 36.8%; adjusted risk ratio = 1.20; 95% confidence interval, 1.06-1.36; *P* = .005).** Birthweight and preterm birth incidence did not substantially differ between women with diarrhea during pregnancy and those without.

CONCLUSIONS:
Diarrheal illness during pregnancy was associated with a higher risk of SGA infants in this rural South Asian population. Interventions to reduce the burden of diarrheal illness during pregnancy may have an impact on SGA births in resource-limited settings.

Implement Sci. 2019 Apr 18;14(1):38. doi: 10.1186/s13012-019-0885-3. (Open access available)

Exploring the effect of implementation and context on a stepped-wedge randomised controlled trial of a vital sign triage device in routine maternity care in low-resource settings.

Vousden N, Lawley E, Seed PT, Gidiri MF, Charantimath U, Makonyola G, Brown A, Yadeta L, Best R, Chinkoyo S, Vwalika B, Nakimuli A, Ditai J, Greene G, Chappell LC, Sandall J, Shennan AH; CRADLE Trial Collaborative Group.

BACKGROUND:
Interventions aimed at reducing maternal mortality are increasingly complex. Understanding how complex interventions are delivered, to whom, and how they work is key in ensuring

their rapid scale-up. We delivered a vital signs triage intervention into routine maternity care in eight low- and middle-income countries with the aim of reducing a composite outcome of morbidity and mortality. This was a pragmatic, hybrid effectiveness-implementation stepped-wedge randomised controlled trial. In this study, we present the results of the mixed-methods process evaluation. The aim was to describe implementation and local context and integrate results to determine whether differences in the effect of the intervention across sites could be explained.

METHODS:
The duration and content of implementation, uptake of the intervention and its impact on clinical management were recorded. These were integrated with interviews (n = 36) and focus groups (n = 19) at 3 months and 6-9 months after implementation. In order to determine the effect of implementation on effectiveness, measures were ranked and averaged across implementation domains to create a composite implementation strength score and then correlated with the primary outcome.

RESULTS:
Overall, 61.1% (n = 2747) of health care providers were trained in the intervention (range 16.5% to 89.2%) over a mean of 10.8 days. Uptake and acceptability of the intervention was good. All clusters demonstrated improved availability of vital signs equipment. There was an increase in the proportion of women having their blood pressure measured in pregnancy following the intervention (79.2% vs. 97.6%; OR 1.30 (1.29-1.31)) and no significant change in referral rates (3.7% vs. 4.4% OR 0.89; (0.39-2.05)). Availability of resources and acceptable, effective referral systems influenced health care provider interaction with the intervention. There was no correlation between process measures within or between domains, or between the composite score and the primary outcome.

CONCLUSIONS:
This process evaluation has successfully described the quantity and quality of implementation. Variation in implementation and context did not explain differences in the effectiveness of the intervention on maternal mortality and morbidity. We suggest future trials should prioritise in-depth evaluation of local context and clinical pathways.

Lancet Glob Health. 2019 Mar;7(3):e347-e356. doi: 10.1016/S2214-109X(18)30526-6. (Open access available)

Effect of a novel vital sign device on maternal mortality and morbidity in low-resource settings: a pragmatic, stepped-wedge, cluster-randomised controlled trial.

Vousden N, Lawley E, Nathan HL, Seed PT, Gidiri MF, Goudar S, Sandall J, Chappell LC, Shennan AH; CRADLE Trial Collaborative Group.

BACKGROUND:

In 2015, an estimated 303 000 women died in pregnancy and childbirth. Obstetric haemorrhage, sepsis, and hypertensive disorders of pregnancy account for more than 50% of maternal deaths worldwide. There are effective treatments for these pregnancy complications, but they require early detection by measurement of vital signs and timely administration to save lives. The primary aim of this trial was to determine whether implementation of the CRADLE Vital Sign Alert and an education package into community and facility maternity care in low-resource settings could reduce a composite of all-cause maternal mortality or major morbidity (eclampsia and hysterectomy).

METHODS:
We did a pragmatic, stepped-wedge, cluster-randomised controlled trial in ten clusters across Africa, India, and Haiti, introducing the device into routine maternity care. Each cluster contained at least one secondary or tertiary hospital and their main referral facilities. Clusters crossed over from existing routine care to the CRADLE intervention in one of nine steps at 2-monthly intervals, with CRADLE devices replacing existing equipment at the randomly allocated timepoint. A computer-generated randomly allocated sequence determined the order in which the clusters received the intervention. Because of the nature of the intervention, this trial was not masked. Data were gathered monthly, with 20 time periods of 1 month. The primary composite outcome was at least one of eclampsia, emergency hysterectomy, and maternal death. This study is registered with the ISRCTN registry, number ISRCTN41244132.

FINDINGS:
Between April 1, 2016, and Nov 30, 2017, among 536 223 deliveries, the primary outcome occurred in 4067 women, with 998 maternal deaths, 2692 eclampsia cases, and 681 hysterectomies. There was an 8% decrease in the primary outcome from 79·4 per 10 000 deliveries pre-intervention to 72·8 per 10 000 deliveries post-intervention (odds ratio [OR] 0·92, 95% CI 0·86-0·97; p=0·0056). After planned adjustments for variation in event rates between and within clusters over time, the unexpected degree of variability meant we were unable to judge the benefit or harms of the intervention (OR 1·22, 95% CI 0·73-2·06; p=0·45).

INTERPRETATION:
There was an absolute 8% reduction in primary outcome during the trial, with no change in resources or staffing, but this reduction could not be directly attributed to the intervention due to variability. We encountered unanticipated methodological challenges with this trial design, which can provide valuable learning for future research and inform the trial design of future international stepped-wedge trials.

PLoS Med. 2019 Apr 12;16(4):e1002783. doi: 10.1371/journal.pmed.1002783. eCollection 2019 Apr. (Open access available)

The incidence of pregnancy hypertension in India, Pakistan, Mozambique, and Nigeria: A prospective population-level analysis.

Magee LA, Sharma S, Nathan HL, Adetoro OO, Bellad MB, Goudar S, Macuacua SE, Mallapur A, Qureshi R, Sevene E, Sotunsa J, Valá A, Lee T, Payne BA, Vidler M, Shennan AH, Bhutta ZA, von Dadelszen P; CLIP Study Group.
Pakistan, Mozambique, Nigeria

BACKGROUND:
Most pregnancy hypertension estimates in less-developed countries are from cross-sectional hospital surveys and are considered overestimates. We estimated population-based rates by standardised methods in 27 intervention clusters of the Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials.

METHODS AND FINDINGS:
CLIP-eligible pregnant women identified in their homes or local primary health centres (2013-2017). Included here are women who had delivered by trial end and received a visit from a community health worker trained to provide supplementary hypertension-oriented care, including standardised blood pressure (BP) measurement. Hypertension (BP ≥ 140/90 mm Hg) was defined as chronic (first detected at <20 weeks gestation) or gestational (≥20 weeks); pre-eclampsia was gestational hypertension plus proteinuria or a pre-eclampsia-defining complication. A multi-level regression model compared hypertension rates and types between countries ($p < 0.05$ considered significant). In 28,420 pregnancies studied, women were usually young (median age 23-28 years), parous (53.7%-77.3%), with singletons (≥97.5%), and enrolled at a median gestational age of 10.4 (India) to 25.9 weeks (Mozambique). Basic education varied (22.8% in Pakistan to 57.9% in India). Pregnancy hypertension incidence was lower in Pakistan (9.3%) than India (10.3%), Mozambique (10.9%), or Nigeria (10.2%) ($p = 0.001$). Most hypertension was diastolic only (46.4% in India, 72.7% in Pakistan, 61.3% in Mozambique, and 63.3% in Nigeria). At first presentation with elevated BP, gestational hypertension was most common diagnosis (particularly in Mozambique [8.4%] versus India[6.9%], Pakistan [6.5%], and Nigeria [7.1%]; $p < 0.001$), followed by pre-eclampsia (India [3.8%], Nigeria [3.0%], Pakistan [2.4%], and Mozambique [2.3%]; $p < 0.001$) and chronic hypertension (especially in Mozambique [2.5%] and Nigeria [2.8%], compared with India [1.2%] and Pakistan [1.5%]; $p < 0.001$). Inclusion of additional diagnoses of hypertension and related complications, from household surveys or facility record review (unavailable in Nigeria), revealed higher hypertension incidence: 14.0% in India, 11.6% in Pakistan, and 16.8% in Mozambique; eclampsia was rare (<0.5%).

CONCLUSIONS:
Pregnancy hypertension is common in less-developed settings. Most women in this study presented with gestational hypertension amenable to surveillance and timed delivery to improve outcomes.

J Obstet Gynaecol India. 2019 Feb;69(1):13-24. doi: 10.1007/s13224-018-1191-8. Epub 2019 Jan 17.

Parenteral Versus Oral Iron for Treatment of Iron Deficiency Anaemia During Pregnancy and post-partum: A Systematic Review.

Radhika AG, Sharma AK, Perumal V, Sinha A, Sriganesh V, Kulshreshtha V, Kriplani A.

INTRODUCTION:
The burden of iron deficiency anaemia during pregnancy and post-partum continues to remain high especially in India. Challenges to treatment include gastrointestinal side effects and non compliance to oral iron therapy. Newer parenteral formulations need to be explored as alternatives.

METHODS:
Meta-analysis of randomized controlled trials published between years 2011 and 2018 comparing anaemic pregnant and post-partum women treated with intravenous iron sucrose versus oral iron was performed. The primary outcomes were mean maternal haemoglobin, serum ferritin and haematocrit at the end of 1st, 2nd, 4th and 6th weeks and comparison of adverse effects.

RESULTS:
Eighteen studies including 1633 antenatal women were randomly assigned to intravenous iron sucrose (*n* = 821) or oral iron [ferrous sulphate, ferrous ascorbate or fumarate] group (*n* = 812) in ten trials . Another eight studies compared iron sucrose infusion with oral iron in 713 post-partum womenwho were randomly assigned to intravenous iron sucrose group (*n* = 351) or oral iron group (*n* = 362). Cumulative analysis of all the time points indicates that the estimated mean values of Hb in the intravenous iron sucrose and oral iron groups were 10.11 g/dl and 9.33 g/dl, respectively, in antenatal group, while it was 10.57 g/dl and 9.74 g/dl in post-partum. The estimated mean ferritin level from first week to six weeks was 63.1 µg/l and 28.6 µg/l, respectively, in intravenous and oral iron groups. Cumulative estimate of haematocrit in the intravenous sucrose and oral iron over 6 weeks showed that the mean values in the respective groups were 30.5% and 29.5% in antenatal and 33.8% and 31.6%, respectively, in post-partum groups. Sensitivity analysis confirmed the reliability and consistency of the results. Oral iron was associated with significant gastrointestinal side effects. There was no significant difference in birthweight between the groups.

CONCLUSION:
This meta-analysis demonstrates that intravenous iron sucrose is more effective than oral iron therapy for pregnant and post-partum women with iron deficiency anaemia. It is an effective and safe alternative to address the problem of iron deficiency especially in those who require rapid replacement of iron stores though medical personnel for intravenous administration of drug is required.*Trial registration* CRD42015024343.

Lancet Glob Health. 2019 May;7(5):e655-e663. doi: 10.1016/S2214-109X(19)30075-0. Epub 2019 Mar 22. (Open access available)

A multifaceted intervention to improve syphilis screening and treatment in pregnant women in Kinshasa, Democratic Republic of the Congo and in Lusaka, Zambia: a cluster randomised controlled trial.

Althabe F, Chomba E, Tshefu AK, Banda E, Belizán M, Bergel E, Berrueta M, Bertrand J, Bose C, Cafferata ML, Carlo WA, Ciganda A, Donnay F, García Elorrio E, Gibbons L, Klein K, Liljestrand J, Lusamba PD, Mavila AK, Mazzoni A, Nkamba DM, Mwanakalanga FH, Mwapule Tembo A, Mwenechanya M, Pyne-Mercier L, Spira C, Wetshikoy JD, Xiong X, Buekens P.

BACKGROUND:
Despite international recommendations, coverage of syphilis testing in pregnant women and treatment of those found seropositive remains limited in sub-Saharan Africa. We assessed whether combining the provision of supplies with a behavioural intervention was more effective than providing supplies only, to improve syphilis screening and treatment during antenatal care.

METHODS:
In this 18-month, cluster randomised controlled trial, we randomly assigned (1:1) 26 urban antenatal care clinics in Kinshasa, Democratic Republic of the Congo, and Lusaka, Zambia, to receive a behavioural intervention (opinion leader selection, academic detailing visits, reminders, audits and feedback, and supportive supervision) plus supplies for syphilis testing and treatment (intervention group) or to receive supplies only (control group). The primary outcomes were proportion of pregnant women who had syphilis screening out of the total who attended the clinic; and the proportion of women who had treatment with benzathine benzylpenicillin out of those who tested positive for syphilis at their first antenatal care visit. This trial is registered at ClinicalTrials.gov, number NCT02353117.

FINDINGS:
The 18-month study period was Feb 1, 2016, to July 14, 2017. 18 357 women were enrolled at the 13 intervention clinics and 17 679 women were enrolled at the 13 control clinics at their first antenatal care visit. Syphilis screening was done in a median of 99·9% (IQR 99·0-100·0) of women in the intervention clinics and 93·8% (85·0-98·9) in the control clinics (absolute difference 6·1% [95% CI 1·1-14·1]; p=0·00092). Syphilis treatment at the first visit was done in a median of 100% (IQR 99·7-100·0) of seropositive women in intervention clinics and 43·2% (2·6-83·2) of seropositive women in control clinics (absolute difference 56·8% [12·8-99·0]; p=0·0028).

INTERPRETATION:
A behavioural intervention, together with the provision of supplies, can lead to more than 95% of women being screened and treated for syphilis. The sole provision of supplies is sufficient to reach such levels of screening coverage but is not sufficient to ensure high levels of treatment.

BMC Pregnancy Childbirth. 2018 Aug 10;18(1):327. doi: 10.1186/s12884-018-1964-1. (Open access available)

Systematic review of community participation interventions to improve maternal health outcomes in rural South Asia.

Sharma BB, Jones L, Loxton DJ, Booth D, Smith R.
Australia

BACKGROUND:
This is a systematic review on the effectiveness of community interventions in improving maternal health care outcomes in South Asia.

METHODS:
We searched electronic databases to June 2017. Randomised or cluster randomised studies in communities within rural/remote areas of Nepal, Bangladesh, India and Pakistan were included. Data were analysed as risk ratios (RR) or odds ratios (OR), and effects were adjusted for clustering. Meta-analyses were performed using random-effects and evidence quality was assessed.

RESULTS:
Eleven randomised trials were included from 5440 citations. Meta-analysis of all community interventions combined compared with control showed a small improvement in the number of women attending at least one antenatal care visit (RR 1.19, 95% CI 1.06 to 1.33). Two community mobilisation sub groups: home care using both male and female mobilisers, and education by community mobilisers, improved the number of women attending at least one antenatal visit. There was no difference in the number of women attending at least one antenatal visit for any other subgroup. There was no difference in the number of women attending 3 or more antenatal visits for all community interventions combined, or any community subgroup. Likewise, there was no difference in attendance at birth between all community interventions combined and control. Health care facility births were modestly increased in women's education groups (adjusted RR (1.15, 95% CI 1.11 to 1.20; 2 studies)). Risk of maternal deaths after 2 years (RR 0.63, 95% CI 0.24 to 1.64; 5 studies), and 3 years (RR 1.11, 95% CI 0.52 to 2.36; 2 studies), were no different between women's education groups and control. Community level mobilisation rather than health care messages at district level improved the numbers of women giving birth at health care facilities (RR1.09 (95%CI 1.06 to 1.13; 1 study)). Maternal health care knowledge scores improved in two community-based interventions, one involving education of male community members.

CONCLUSION:
Women's education interventions may improve the number of women seeking birth at a health care facility, but the evidence is of low quality. No impact on maternal mortality was observed Future research should explore the effectiveness of including male mobilisers.

Maternal malaria prevention

Malar J. 2019 Mar 28;18(1):105. doi: 10.1186/s12936-019-2737-7. (Open access available)

Artemisinin-based combination therapy during pregnancy: outcome of pregnancy and infant mortality: a cohort study.

Nambozi M, Tinto H, Mwapasa V, Tagbor H, Kabuya JB, Hachizovu S, Traoré M, Valea I, Tahita MC, Ampofo G, Buyze J, Ravinetto R, Arango D, Thriemer K, Mulenga M, van Geertruyden JP, D'Alessandro U.

Burkina Faso, Ghana, Malawi and Zambia

BACKGROUND:
The World Health Organization (WHO) recommendation of treating uncomplicated malaria during the second and third trimester of pregnancy with an artemisinin-based combination therapy (ACT) has already been implemented by all sub-Saharan African countries. However, there is limited knowledge on the effect of ACT on pregnancy outcomes, and on newborn and infant's health.

METHODS:
Pregnant women with malaria in four countries (Burkina Faso, Ghana, Malawi and Zambia) were treated with either artemether-lumefantrine (AL), amodiaquine-artesunate (ASAQ), mefloquine-artesunate (MQAS), or dihydroartemisinin-piperaquine (DHA-PQ); 3127 live new-borns (822 in the AL, 775 in the ASAQ, 765 in the MQAS and 765 in the DHAPQ arms) were followed-up until their first birthday.

RESULTS:
Prevalence of placental malaria and low birth weight were 28.0% (738/2646) and 16.0% (480/2999), respectively, with no significant differences between treatment arms. No differences in congenital malformations (p = 0.35), perinatal mortality (p = 0.77), neonatal mortality (p = 0.21), and infant mortality (p = 0.96) were found.

CONCLUSIONS:
Outcome of pregnancy and infant survival were similar between treatment arms indicating that any of the four artemisinin-based combinations could be safely used during the second and third trimester of pregnancy without any adverse effect on the baby. Nevertheless, smaller safety differences between artemisinin-based combinations cannot be excluded; country-wide post-marketing surveillance would be very helpful to confirm such findings.

Lancet. 2019 Apr 6;393(10179):1428-1439. doi: 10.1016/S0140-6736(18)32224-4. Epub 2019 Mar 22. (Open access available)

Monthly sulfadoxine-pyrimethamine versus dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomised, controlled, superiority trial.

Kajubi R, Ochieng T, Kakuru A, Jagannathan P, Nakalembe M, Ruel T, Opira B, Ochokoru H, Ategeka J, Nayebare P, Clark TD, Havlir DV, Kamya MR, Dorsey G.

Nigeria

BACKGROUND:
Intermittent treatment with sulfadoxine-pyrimethamine, recommended for prevention of malaria in pregnant women throughout sub-Saharan Africa, is threatened by parasite resistance. We assessed the efficacy and safety of intermittent preventive treatment with dihydroartemisinin-piperaquine as an alternative to sulfadoxine-pyrimethamine.

METHODS:
We did a double-blind, randomised, controlled, superiority trial at one rural site in Uganda with high malaria transmission and sulfadoxine-pyrimethamine resistance. HIV-uninfected pregnant women between 12 and 20 weeks gestation were randomly assigned (1:1) to monthly intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine or dihydroartemisinin-piperaquine. The primary endpoint was the risk of a composite adverse birth outcome defined as lowbirthweight, preterm birth, or small for gestational age in livebirths. Protective efficacy was defined as 1-prevalence ratio or 1-incidence rate ratio. All analyses were done by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02793622.

FINDINGS:
Between Sept 6, 2016, and May 29, 2017, 782 women were enrolled and randomly assigned to receive sulfadoxine-pyrimethamine (n=391) or dihydroartemisinin-piperaquine (n=391); 666 (85·2%) women who delivered livebirths were included in the primary analysis. There was no significant difference in the risk of our composite adverse birth outcome between the dihydroartemisinin-piperaquine and sulfadoxine-pyrimethamine treatment group (54 [16%] of 337 women vs 60 [18%] of 329 women; protective efficacy 12% [95% CI -23 to 37], p=0·45). Both drug regimens were well tolerated, with no significant differences in adverse events between the groups, with the exception of asymptomatic corrected QT interval prolongation, which was significantly higher in the dihydroartemisinin-piperaquine group (mean change 13 ms [SD 23]) than in the sulfadoxine-pyrimethamine group (mean change 0 ms [SD 23]; p<0·0001).

INTERPRETATION:
Monthly intermittent preventive treatment with dihydroartemisinin-piperaquine was safe but did not lead to significant improvements in birth outcomes compared with sulfadoxine-pyrimethamine.

PLoS Med. 2018 Jul 17;15(7):e1002606. doi: 10.1371/journal.pmed.1002606. eCollection 2018 Jul. (Open access available)

Dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria during pregnancy and risk of malaria in early childhood: A randomized controlled trial.

Jagannathan P, Kakuru A, Okiring J, Muhindo MK, Natureeba P, Nakalembe M, Opira B, Olwoch P, Nankya F, Ssewanyana I, Tetteh K, Drakeley C, Beeson J, Reiling L, Clark TD,

Rodriguez-Barraquer I, Greenhouse B, Wallender E, Aweeka F, Prahl M, Charlebois ED, Feeney ME, Havlir DV, Kamya MR, Dorsey G.
USA, Uganda, UK, Australia

BACKGROUND:
Intermittent preventive treatment of malaria in pregnancy (IPTp) with dihydroartemisinin-piperaquine (IPTp-DP) has been shown to reduce the burden of malaria during pregnancy compared to sulfadoxine-pyrimethamine (IPTp-SP). However, limited data exist on how IPTp regimens impact malaria risk during infancy. We conducted a double-blinded randomized controlled trial (RCT) to **test the hypothesis that children born to mothers given IPTp-DP would have a lower incidence of malaria during infancy compared to children born to mothers who received IPTp-SP**.

METHODS AND FINDINGS:
We compared malaria metrics among children in Tororo, Uganda, born to women randomized to IPTp-SP given every 8 weeks (SP8w, n = 100), IPTp-DP every 8 weeks (DP8w, n = 44), or IPTp-DP every 4 weeks (DP4w, n = 47). After birth, children were given chemoprevention with DP every 12 weeks from 8 weeks to 2 years of age. **The primary outcome was incidence of malaria during the first 2 years of life.** Secondary outcomes included time to malaria from birth and time to parasitemia following each dose of DP given during infancy. Results are reported after adjustment for clustering (twin gestation) and potential confounders (maternal age, gravidity, and maternal parasitemia status at enrolment).The study took place between June 2014 and May 2017. **Compared to children whose mothers were randomized to IPTp-SP8w (0.24 episodes per person year [PPY]), the incidence of malaria was higher in children born to mothers who received IPTp-DP4w (0.42 episodes PPY, adjusted incidence rate ratio [aIRR] 1.92; 95% CI 1.00-3.65, p = 0.049) and nonsignificantly higher in children born to mothers who received IPT-DP8w (0.30 episodes PPY, aIRR 1.44; 95% CI 0.68-3.05, p = 0.34).** However, these associations were modified by infant sex. Female children whose mothers were randomized to IPTp-DP4w had an apparently 4-fold higher incidence of malaria compared to female children whose mothers were randomized to IPTp-SP8w (0.65 versus 0.20 episodes PPY, aIRR 4.39, 95% CI 1.87-10.3, p = 0.001), but no significant association was observed in male children (0.20 versus 0.28 episodes PPY, aIRR 0.66, 95% CI 0.25-1.75, p = 0.42). Nonsignificant increases in malaria incidence were observed among female, but not male, children born to mothers who received DP8w versus SP8w. In exploratory analyses, levels of malaria-specific antibodies in cord blood were similar between IPTp groups and sex. However, female children whose mothers were randomized to IPTp-DP4w had lower mean piperaquine (PQ) levels during infancy compared to female children whose mothers received IPTp-SP8w (coef 0.81, 95% CI 0.65-1.00, p = 0.048) and male children whose mothers received IPTp-DP4w (coef 0.72, 95% CI 0.57-0.91, p = 0.006). There were no significant sex-specific differences in PQ levels among children whose mothers were randomized to IPTp-SP8w or IPTp-DP8w. The main limitations were small sample size and childhood provision of DP every 12 weeks in infancy.

CONCLUSIONS:
Contrary to our hypothesis, preventing malaria in pregnancy with IPTp-DP in the context of chemoprevention with DP during infancy does not lead to a reduced incidence of malaria in childhood; in this setting, it may be associated with an increased incidence of malaria in

females. Future studies are needed to better understand the biological mechanisms of in utero drug exposure on drug metabolism and how this may affect the dosing of antimalarial drugs for treatment and prevention during infancy.

Malar J. 2018 Jul 6;17(1):251. doi: 10.1186/s12936-018-2394-2. (Open access available)

Intermittent screening and treatment with artemether-lumefantrine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in pregnancy: a facility-based, open-label, non-inferiority trial in Nigeria.

Esu E, Berens-Riha N, Pritsch M, Nwachuku N, Loescher T, Meremikwu M.
Germany, Nigeria

BACKGROUND:
The spread of SP resistance may compromise the effectiveness of intermittent preventive treatment of malaria in pregnancy (MiP) with sulfadoxine-pyrimethamine (IPTp-SP) across Africa. However, there is no recommended alternative medicine for IPTp or alternative strategy for prevention of MiP. This poses problems for the prevention of MiP. **This study investigated, whether screening with a rapid diagnostic test for malaria at routine antenatal clinic attendances and treatment of only those who are positive (intermittent screening and treatment) with artemether-lumefantrine is as effective and safe as IPTp-SP in pregnant women**.

METHODS:
During antenatal clinic sessions at the General Hospital Calabar, Nigeria, held between October 2013 and November 2014, 459 pregnant women were randomized into either the current standard IPTp-SP or intermittent screening and treatment with artemether-lumefantrine (ISTp-AL). All women received a long-lasting insecticide-treated net at enrolment. Study women had a maximum of four scheduled visits following enrolment. Haemoglobin concentration and peripheral parasitaemia were assessed in the third trimester (36-40 weeks of gestation). Birth weight was documented at delivery or within a week for babies delivered at home.

RESULTS:
In the third trimester, the overall prevalence of severe anaemia (Hb < 8 g/dl) and moderate (8-10.9 g/dl) anaemia was 0.8 and 27.7%, respectively, and was similar in both treatment groups (p = 0.204). The risk of third-trimester severe anaemia did not differ significantly between both treatment arms (risk difference - 1.75% [95% CI - 4.16 to 0.66]) although the sample was underpowered for this outcome due to several participants being unavailable to give a blood sample. The risk of third-trimester maternal parasitaemia was significantly lower in the ISTp-AL arm (RD - 3.96% [95% CI - 7.76 to - 0.16]). **The risk of low birthweight was significantly lower in the ISTp-AL arm after controlling for maternal age, gravidity and baseline parasitaemia (risk difference - 1.53% [95% CI - 1.54 to - 1.15]).** Women in the ISTp-AL arm complained of fever more frequently compared to women in the IPTp-SP arm (p = 0.022).

CONCLUSIONS:
The trial results suggest that in an area of high malaria transmission with moderate sulfadoxine-pyrimethamine resistance, ISTp with artemether-lumefantrine may be an effective strategy for controlling malaria in pregnancy.

Vector Borne Dis. 2018 Jul-Sep;55(3):197-202. doi: 10.4103/0972-9062.249128. (Open access available)

Comparison of the effectiveness of two-dose *versus* three-dose sulphadoxine-pyrimethamine in preventing adverse pregnancy outcomes in Nigeria.

Igboeli NU, Adibe MO, Ukwe CV, Aguwa CN.
Nigeria

Background & objectives:
Three doses of intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) has been adopted as the new recommendation for prevention of malaria in pregnancy. This study evaluated the effectiveness of two-dose versus three-dose of SP for IPTp-SP in the prevention of low birth weight (LBW) and malaria parasitaemia.

Methods:
An open, randomized, controlled, longitudinal trial was conducted in a secondary level hospital in Nsukka region of Enugu State, Nigeria. A sample of 210 pregnant women within gestational ages of 16-24 wk were recruited at antenatal clinics and equally randomized to either a two-dose SP or three-dose SP group. The primary endpoints were LBWs, peripheral, and placental parasitaemia, while the secondary endpoints were maternal anaemia, pre-term birth, clinical malaria and adverse effects of SP.

Results:
Among 207 cases followed till delivery, the prevalence of parasitaemia was lower in three-dose group than in two-dose group for both peripheral (9.3% versus 27.8%) and placental (10.6% versus 25.6%) parasitaemia. The adjusted odds ratios (aOR) were 0.15 [95% confidence interval (CI), 0.05 - 0.45] and 0.17 (95% CI, 0.06-0.51), respectively. The prevalence of LBW was also lower in three-dose (3.5%) than in two-dose (12.2%) group (aOR, 0.15; 95% CI, 0.04-0.63); however, the prevalence of maternal anaemia, pre-term births, clinical malaria and SP adverse effects were similar between the two arms of treatment.

Interpretation & conclusion:
Addition of a third SP dose to the standard two-dose SP for IPTp led to improved reductions in the risk of some adverse pregnancy outcomes.

Lancet Infect Dis. 2018 Oct;18(10):1097-1107. doi: 10.1016/S1473-3099(18)30415-8. Epub 2018 Sep 5. (Open access available)

Chloroquine as weekly chemoprophylaxis or intermittent treatment to prevent malaria in pregnancy in Malawi: a randomised controlled trial.

Divala TH, Mungwira RG, Mawindo PM, Nyirenda OM, Kanjala M, Ndaferankhande M, Tsirizani LE, Masonga R, Muwalo F, Boudová S, Potter GE, Kennedy J, Goswami J, Wylie BJ, Muehlenbachs A, Ndovie L, Mvula P, Mbilizi Y, Tomoka T, Laufer MK.

Author information

Malawi, USA

BACKGROUND:
Sulfadoxine-pyrimethamine resistance threatens efficacy of intermittent preventive treatment of malaria during pregnancy, and alternative regimens need to be identified. With the return of chloroquine efficacy in southern Africa, we postulated that chloroquine either as an intermittent therapy or as weekly chemoprophylaxis would be more efficacious than intermittent sulfadoxine-pyrimethamine for prevention of malaria in pregnancy and associated maternal and newborn adverse outcomes.

METHODS:
We did an open-label, single-centre, randomised controlled trial at Ndirande Health Centre, Blantyre, in southern Malawi. We enrolled pregnant women (first or second pregnancy) at 20-28 weeks' gestation who were HIV negative. Participants were randomly assigned in a 1:1:1 ratio using a computer-generated list to either **intermittent sulfadoxine-pyrimethamine (two doses of 1500 mg sulfadoxine and 75 mg pyrimethamine, 4 weeks apart), intermittent chloroquine (two doses of 600 mg on day 1, 600 mg on day 2, and 300 mg on day 3), or chloroquine prophylaxis (600 mg on day 1 then 300 mg every week).** The primary endpoint was placental malaria in the modified intent-to-treat population, which consisted of participants who contributed placental histopathology data at birth. Secondary outcomes included clinical malaria, maternal anaemia, low birthweight, and safety. This trial is registered with ClinicalTrials.gov, number NCT01443130.

FINDINGS:
Between February, 2012, and May, 2014, we enrolled and randomly allocated 900 women, of whom 765 contributed histopathological data and were included in the primary analysis. 108 (14%) women had placental malaria, which was lower than the anticipated prevalence of placental malaria infection. **Protection from placental malaria was not improved by chloroquine as either prophylaxis (30 [12%] of 259 had positive histopathology; relative risk [RR] 0·75, 95% CI 0·48-1·17) or intermittent therapy (39 [15%] of 253; RR 1·00, 0·67-1·50) compared with intermittent sulfadoxine-pyrimethamine (39 [15%] of 253).** In protocol-specified analyses adjusted for maternal age, gestational age at enrolment, bednet use the night before enrolment, anaemia at enrolment, and malaria infection at enrolment, women taking chloroquine as prophylaxis had 34% lower placental infections than did those allocated intermittent sulfadoxine-pyrimethamine (RR 0·66, 95% CI 0·46-0·95). **Clinical malaria was reported in nine women assigned intermittent sulfadoxine-pyrimethamine, four allocated intermittent chloroquine (p=0·26), and two allocated**

chloroquine prophylaxis (p=0·063). Maternal anaemia was noted in five women assigned intermittent sulfadoxine-pyrimethamine, 15 allocated intermittent chloroquine (p=0·038), and six assigned chloroquine prophylaxis (p>0·99). **Low birthweight was recorded for 31 babies born to women allocated intermittent sulfadoxine-pyrimethamine, 29 assigned intermittent chloroquine (p=0·78), and 41 allocated chloroquine prophylaxis (p=0·28). Four women assigned intermittent sulfadoxine-pyrimethamine had adverse events possibly related to study product compared with 94 women allocated intermittent chloroquine (p<0·0001) and 26 allocated chloroquine prophylaxis (p<0·0001). Three women had severe or life-threatening adverse events related to study product, of whom all were assigned intermittent chloroquine (p=0·25)**.

INTERPRETATION:
Chloroquine administered as intermittent therapy did not provide better protection from malaria and related adverse effects compared with intermittent sulfadoxine-pyrimethamine in a setting of high resistance to sulfadoxine-pyrimethamine. Chloroquine chemoprophylaxis might provide benefit in protecting against malaria during pregnancy, but studies with larger sample sizes are needed to confirm these results.

Cochrane Database Syst Rev. 2018 Nov 14;11:CD011444. doi: 10.1002/14651858.CD011444.pub3. (Open access available)

Mefloquine for preventing malaria in pregnant women.

González R, Pons-Duran C, Piqueras M, Aponte JJ, Ter Kuile FO, Menéndez C.
Spain

BACKGROUND:
The World Health Organization recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine for malaria for all women who live in moderate to high malaria transmission areas in Africa. However, parasite resistance to sulfadoxine-pyrimethamine has been increasing steadily in some areas of the region. Moreover, HIV-infected women on cotrimoxazole prophylaxis cannot receive sulfadoxine-pyrimethamine because of potential drug interactions. Thus, there is an urgent need to identify alternative drugs for prevention of malaria in pregnancy. One such candidate is mefloquine.

OBJECTIVES:
To assess the effects of mefloquine for preventing malaria in pregnant women, specifically, to evaluate: the efficacy, safety, and tolerability of mefloquine for preventing malaria in pregnant women; and the impact of HIV status, gravidity, and use of insecticide-treated nets on the effects of mefloquine.

SEARCH METHODS:
We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, Latin American Caribbean Health Sciences Literature (LILACS), the Malaria in Pregnancy

Library, and two trial registers up to 31 January 2018. In addition, we checked references and contacted study authors to identify additional studies, unpublished data, confidential reports, and raw data from published trials.

SELECTION CRITERIA:
Randomized and quasi-randomized controlled trials comparing mefloquine IPT or mefloquine prophylaxis against placebo, no treatment, or an alternative drug regimen.

DATA COLLECTION AND ANALYSIS:
Two review authors independently screened all records identified by the search strategy, applied inclusion criteria, assessed risk of bias, and extracted data. We contacted trial authors to ask for additional information when required. Dichotomous outcomes were compared using risk ratios (RRs), count outcomes as incidence rate ratios (IRRs), and continuous outcomes using mean differences (MDs). We have presented all measures of effect with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach for the following main outcomes of analysis: maternal peripheral parasitaemia at delivery, clinical malaria episodes during pregnancy, placental malaria, maternal anaemia at delivery, low birth weight, spontaneous abortions and stillbirths, dizziness, and vomiting.

MAIN RESULTS:
Six trials conducted between 1987 and 2013 from Thailand (1), Benin (3), Gabon (1), Tanzania (1), Mozambique (2), and Kenya (1) that included 8192 pregnant women met our inclusion criteria.Two trials (with 6350 HIV-uninfected pregnant women) compared two IPTp doses of mefloquine with two IPTp doses of sulfadoxine-pyrimethamine. Two other trials involving 1363 HIV-infected women compared three IPTp doses of mefloquine plus cotrimoxazole with cotrimoxazole. One trial in 140 HIV-infected women compared three doses of IPTp-mefloquine with cotrimoxazole. Finally, one trial enrolling 339 of unknown HIV status compared mefloquine prophylaxis with placebo.Study participants included women of all gravidities and of all ages (four trials) or > 18 years (two trials). Gestational age at recruitment was > 20 weeks (one trial), between 16 and 28 weeks (three trials), or ≤ 28 weeks (two trials). Two of the six trials blinded participants and personnel, and only one had low risk of detection bias for safety outcomes.When compared with sulfadoxine-pyrimethamine, IPTp-mefloquine results in a 35% reduction in maternal peripheral parasitaemia at delivery (RR 0.65, 95% CI 0.48 to 0.86; 5455 participants, 2 studies; high-certainty evidence) but may have little or no effect on placental malaria infections (RR 1.04, 95% CI 0.58 to 1.86; 4668 participants, 2 studies; low-certainty evidence). Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy (incidence rate ratio (IRR) 0.83, 95% CI 0.65 to 1.05, 2 studies; high-certainty evidence). Mefloquine decreased maternal anaemia at delivery (RR 0.84, 95% CI 0.76 to 0.94; 5469 participants, 2 studies; moderate-certainty evidence). Data show little or no difference in the proportions of low birth weight infants (RR 0.95, 95% CI 0.78 to 1.17; 5641 participants, 2 studies; high-certainty evidence) and in stillbirth and spontaneous abortion rates (RR 1.20, 95% CI 0.91 to 1.58; 6219 participants, 2 studies; I statistic = 0%; moderate-certainty evidence). IPTp-mefloquine increased drug-related vomiting (RR 4.76, 95% CI 4.13 to 5.49; 6272 participants, 2 studies; high-certainty evidence) and dizziness (RR 4.21, 95% CI 3.36 to 5.27; participants = 6272, 2 studies; moderate-certainty evidence).When compared with cotrimoxazole, IPTp-mefloquine

plus cotrimoxazole probably results in a 48% reduction in maternal peripheral parasitaemia at delivery (RR 0.52, 95% CI 0.30 to 0.93; 989 participants, 2 studies; moderate-certainty evidence) and a 72% reduction in placental malaria (RR 0.28, 95% CI 0.14 to 0.57; 977 participants, 2 studies; moderate-certainty evidence) but has little or no effect on the incidence of clinical malaria episodes during pregnancy (IRR 0.76, 95% CI 0.33 to 1.76, 1 study; high-certainty evidence) and probably no effect on maternal anaemia at delivery (RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 studies; moderate-certainty evidence), low birth weight rates (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 studies; moderate-certainty evidence), and rates of spontaneous abortion and stillbirth (RR 1.12, 95% CI 0.42 to 2.98; 1347 participants, 2 studies; very low-certainty evidence). Mefloquine was associated with higher risks of drug-related vomiting (RR 7.95, 95% CI 4.79 to 13.18; 1055 participants, one study; high-certainty evidence) and dizziness (RR 3.94, 95% CI 2.85 to 5.46; 1055 participants, 1 study; high-certainty evidence).

AUTHORS' CONCLUSIONS:
Mefloquine was more efficacious than sulfadoxine-pyrimethamine in HIV-uninfected women or daily cotrimoxazole prophylaxis in HIV-infected pregnant women for prevention of malaria infection and was associated with lower risk of maternal anaemia, no adverse effects on pregnancy outcomes (such as stillbirths and abortions), and no effects on low birth weight and prematurity. However, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

Malar J. 2019 Feb 20;18(1):41. doi: 10.1186/s12936-019-2676-3. (Open access available)

Effects of a health educational intervention on malaria knowledge, motivation, and behavioural skills: a randomized controlled trial.

Balami AD, Said SM, Zulkefli NAM, Bachok N, Audu B.

BACKGROUND:
The levels of insecticide-treated net use among pregnant women and uptake of intermittent preventive treatment in pregnancy, have been sub-optimal in Nigeria. Previous studies have reported positive correlations between knowledge, attitude and practice of malaria preventive measures. It has also been reported that information and motivation, act through a mediator (behavioural skills), to cause a health behaviour change. The aim of this study was as such to develop, implement, and assess the effects of a health educational intervention based on the information-motivation-behavioural skills (IMB) model on the levels of knowledge, motivation, and behavioural skills for ITN use and IPTp uptake among pregnant women in a hospital in north-eastern Nigeria.

METHODS:
This was a randomized controlled parallel-group trial in which 372 antenatal care attendees were randomly assigned to either an intervention or control group after collecting baseline data using a structured questionnaire. The intervention group received a 4-h health education on malaria, guided by a module developed based on the IMB theory, while the

control group received health education on breastfeeding for a similar duration and by the same facilitator. Follow-up data were subsequently collected at 2 months and at 4 months post-intervention using the same questionnaire. The generalized linear mixed models analysis was used to determine the between-group and within-group effects of the intervention. The intention-to-treat analysis was used after missing data had been replaced. This was followed by a sensitivity analysis, where the analyses were repeated without replacing the missing values.

RESULTS:
The intervention was significant in achieving a 12.75% ($p < 0.001$), 8.55% ($p < 0.001$), and 6.350% ($p < 0.001$) higher total knowledge, motivation, and behavioural skills scores respectively, for the intervention group over the control group. The sensitivity analysis revealed no great differences in the effect sizes, even when missing data were not replaced.

CONCLUSION:
The intervention module was effective in improving knowledge, motivation and behavioural skills. It is as such recommended to be adopted and incorporated into the routine antenatal health education schedules. It is also recommended that booster doses of the module be given say 2 months after the first dose to sustain levels of motivation and behavioural skills

Obstetric care and delivery

BMC Med. 2019 May 2;17(1):87. doi: 10.1186/s12916-019-1320-y. (Open access available)

DECIDE: a cluster-randomized controlled trial to reduce unnecessary caesarean deliveries in Burkina Faso.

Kaboré C, Ridde V, Chaillet N, Yaya Bocoum F, Betrán AP, Dumont A.
Burkina Faso

BACKGROUND:
In Burkina Faso, facility-based caesarean delivery rates have markedly increased since the national subsidy policy for deliveries and emergency obstetric care was implemented in 2006. Effective and safe strategies are needed to prevent unnecessary caesarean deliveries.

METHODS:
We conducted a cluster-randomized controlled trial of a multifaceted intervention at 22 referral hospitals in Burkina Faso. The evidence-based intervention was designed to promote the use of clinical algorithms for caesarean decision-making using in-site training, audits and feedback of caesarean indications and SMS reminders. The primary outcome was the change in the percentage of unnecessary caesarean deliveries. Unnecessary caesareans were defined on the basis of the literature review and expert consensus. Data were collected daily using a standardized questionnaire, in the same way at both the intervention and control hospitals. Caesareans were classified as necessary or unnecessary in the same way, in both arms of the trial using a standardized computer algorithm.

RESULTS:
A total of 2138 and 2036 women who delivered by caesarean section were analysed in the pre and post-intervention periods, respectively. **A significant reduction in the percentage of unnecessary caesarean deliveries was evident from the pre- to post-intervention period in the intervention group compared with the control group (18.96 to 6.56% and 18.27 to 23.30% in the intervention and control groups**, respectively; odds ratio [OR] for incremental change over time, adjusted for hospital and patient characteristics, 0.22; 95% confidence interval [CI], 0.14 to 0.34; P < 0.001; adjusted risk difference, - 17.02%; 95% CI, - 19.20 to - 13.20%). **The intervention did not significantly affect the rate of maternal death (0.75 to 0.19% and 0.92 to 0.40% in the intervention and control groups, respectively; adjusted OR 0.32; 95% CI 0.04 to 2.23; P = 0.253) or intrapartum-related neonatal death (4.95 to 6.32% and 5.80 to 4.29% in the intervention and control groups, respectively, adjusted OR 1.73; 95% CI 0.82 to 3.66; P = 0.149)**. The overall perinatal mortality data were not available.

CONCLUSION:
Promotion and training on clinical algorithms for decision-making, audit and feedback and SMS reminders reduced unnecessary caesarean deliveries, compared with usual care in a low-resource setting.

PLoS One. 2018 Oct 12;13(10):e0204986. doi: 10.1371/journal.pone.0204986. eCollection 2018. (Open access available)

Is deployment of trained nurses to rural villages a remedy for the low skilled birth attendance in Ethiopia? A cluster randomized-controlled community trial.

Zerfu TA, Taddese H, Nigatu T, Tenkolu G, Khan DN, Biadgilign S, Deribew A.
Kenya, Ethiopia, WHO, Switzerland

BACKGROUND:
Low coverage of Skilled Birth Attendance (SBA) is one of the major drivers of maternal mortality in many low- and middle-income countries (LMICs) including Ethiopia. We conducted a cluster-randomized controlled community trial to assess the effect of deploying trained community based nurses to rural communities on the uptake levels of SBA in Ethiopia.

METHODS:
A three-arm, parallel groups, cluster-randomized community trial was conducted to assess the effect of deploying trained community based reproductive health nurses (CORN) on the uptake of SBA services. **A total of 282 villages were randomly selected and assigned to a control arm (n = 94) or 1 of 2 treatment arms (n = 94 each). The treatment groups differed by where these new service providers were deployed, a health post (HP) or health center (HC).** Baseline and end line surveys were conducted to document and

measure the effects of the intervention. Program impacts on SBA coverage were calculated using difference-in-difference (DID) analysis.

RESULTS:
After nine months of intervention, the coverage of SBA services increased significantly by 81.1% (from 24.61 to 44.59) in the HP based intervention arm, and by 122.9% (from 16.41 to 36.59) in the HC arm, respectively (p <0.01). Conversely, a small and non-significant (2%) decline in SBA coverage were observed in the control arm (P >0.05). The DID estimate indicated a net increase in SBA coverage of 21.32 and 20.52 percentage points (PP) across the HP and HC based intervention arms, respectively (p < 0.001).

CONCLUSIONS:
Deployment of trained reproductive health nurses to rural communities in Ethiopia significantly improved utilization of SBA services. Therefore; in similar low income settings where coverage of SBA services is very low, deployment of trained community based nurses to grassroots level could potentiate rapid service uptake. Additional cost-effectiveness and validation studies at various setups are required, before scale-up of the innovation, however.

BMJ Glob Health. 2018 Oct 8;3(5):e000907. doi: 10.1136/bmjgh-2018-000907. eCollection 2018. (Open access available)

Improving quality of care during childbirth in primary health centres: a stepped-wedge cluster-randomised trial in India.

Agarwal R, Chawla D, Sharma M, Nagaranjan S, Dalpath SK, Gupta R, Kumar S, Chaudhuri S, Mohanty P, Sankar MJ, Agarwal K, Rani S, Thukral A, Jain S, Yadav CP, Gathwala G, Kumar P, Sarin J, Sreenivas V, Aggarwal KC, Kumar Y, Kharya P, Bisht SS, Shridhar G, Arora R, Joshi K, Bhalla K, Soni A, Singh S, Devakirubai P, Samuel R, Yadav R, Bahl R, Kumar V, Paul VK; QI Haryana Study Collaboration.
India, WHO, Switzerland.

Background:
Low/middle-income countries need a large-scale improvement in the quality of care (QoC) around the time of childbirth in order to reduce high maternal, fetal and neonatal mortality. However, there is a paucity of scalable models.

Methods:
We conducted a stepped-wedge cluster-randomised trial in 15 primary health centres (PHC) of the state of Haryana in India to test the effectiveness of a multipronged quality management strategy comprising capacity building of providers, periodic assessments of the PHCs to identify quality gaps and undertaking improvement activities for closure of the gaps. The 21-month duration of the study was divided into seven periods (steps) of 3 months each. Starting from the second period, a set of randomly selected three PHCs (cluster) crossed over to the intervention arm for rest of the period of the study. The primary outcomes included the number of women approaching the PHCs for childbirth and 12 directly observed

essential practices related to the childbirth. Outcomes were adjusted with random effect for cluster (PHC) and fixed effect for 'months of intervention'.

Results:
The intervention strategy led to increase in the number of women approaching PHCs for childbirth (26 vs 21 women per PHC-month, adjusted incidence rate ratio: 1.22; 95% CI 1.17 to 1.28). Of the 12 practices, 6 improved modestly, 2 remained near universal during both intervention and control periods, 3 did not change and 1 worsened. There was no evidence of change in mortality with a majority of deaths occurring either during referral transport or at the referral facilities.

Conclusion:
A multipronged quality management strategy enhanced utilisation of services and modestly improved key practices around the time of childbirth in PHCs in India.

Int J Gynaecol Obstet. 2018 Dec;143(3):344-350. doi: 10.1002/ijgo.12648. Epub 2018 Sep 4.

Randomized controlled trial of continuous Doppler versus intermittent fetoscope fetal heart rate monitoring in a low-resource setting.

Mdoe PF, Ersdal HL, Mduma E, Moshiro R, Dalen I, Perlman JM, Kidanto H.
Tanzania, Norway, USA

OBJECTIVE:
To compare the frequency of abnormal fetal heart rate (FHR) detection between continuous Doppler and intermittent fetoscope monitoring.

METHOD:
A randomized controlled open-label trial was conducted between February 1, 2016, and January 31, 2017, at Haydom Lutheran hospital, Tanzania. **Women in active labor with singleton pregnancies and normal FHR at admission were randomly allocated in a 1:1 ratio to receive either continuous or intermittent FHR monitoring**. The primary outcome was abnormal FHR detection.

RESULTS:
2652 women were enrolled; 1340 received continuous monitoring and 1312 received intermittent monitoring. Continuous FHR monitoring detected abnormal FHR in 108 (8.1%) participants versus 40 (3.0%) participants in the intermittent monitoring group (risk ratio [RR] 2.64, 95% confidence interval [CI] 1.8-3.7; P<0.001). The increased detection rate in the continuous versus intermittent monitoring group was associated with an increase in rate of subsequent intrauterine resuscitations (89 [6.6%] vs 42 [3.2%]; RR 2.07, 95% CI 1.4-2.9; P<0.001). In total, 92 (3.5%) infants had adverse perinatal outcomes, with no significant differences between groups.

CONCLUSION:

Continuous FHR monitoring increased identification of abnormal FHR and subsequent intrauterine resuscitations.

PLoS Med. 2019 Mar 29;16(3):e1002775. doi: 10.1371/journal.pmed.1002775. eCollection 2019 Mar. (Open access available)

Incidence of eclampsia and related complications across 10 low- and middle-resource geographical regions: Secondary analysis of a cluster randomised controlled trial.

Vousden N, Lawley E, Seed PT, Gidiri MF, Goudar S, Sandall J, Chappell LC, Shennan AH; CRADLE Trial Collaborative Group.

BACKGROUND:
In 2015, approximately 42,000 women died as a result of hypertensive disorders of pregnancy worldwide; over 99% of these deaths occurred in low- and middle-income countries. **The aim of this paper is to describe the incidence and characteristics of eclampsia and related complications from hypertensive disorders of pregnancy across 10 low- and middle-income geographical regions in 8 countries, in relation to magnesium sulfate availability.**

METHODS AND FINDINGS:
This is a secondary analysis of a stepped-wedge cluster randomised controlled trial undertaken in sub-Saharan Africa, India, and Haiti. This trial implemented a novel vital sign device and training package in routine maternity care with the aim of reducing a composite outcome of maternal mortality and morbidity. Institutional-level consent was obtained, and all womenpresenting for maternity care were eligible for inclusion. Data on eclampsia, stroke, admission to intensive care with a hypertensive disorder of pregnancy, and maternal death from a hypertensive disorder of pregnancy were prospectively collected from routine data sources and active case finding, together with data on perinatal outcomes in women with these outcomes. **In 536,233 deliveries between 1 April 2016 and 30 November 2017, there were 2,692 women with eclampsia (0.5%). In total 6.9% (n = 186; 3.47/10,000 deliveries) of women with eclampsia died, and a further 51 died from other complications of hypertensive disorders of pregnancy (0.95/10,000).** After planned adjustments, the implementation of the CRADLE intervention was not associated with any significant change in the rates of eclampsia, stroke, or maternal death or intensive care admission with a hypertensive disorder of pregnancy. Nearly 1 in 5 (17.9%) women with eclampsia, stroke, or a hypertensive disorder of pregnancy causing intensive care admission or maternal death experienced a stillbirth or neonataldeath. A third of eclampsia cases (33.2%; n = 894) occurred in women under 20 years of age, 60.0% in women aged 20-34 years (n = 1,616), and 6.8% (n = 182) in women aged 35 years or over. Rates of eclampsia varied approximately 7-fold between sites (range 19.6/10,000 in Zambia Centre 1 to 142.0/10,000 in Sierra Leone). Over half (55.1%) of first eclamptic fits occurred in a health-care facility, with the remainder in the community. Place of first fit varied substantially between sites (from 5.9% in the central referral facility in Sierra Leone to 85% in Uganda Centre 2). **On average,**

magnesium sulfate was available in 74.7% of facilities (range 25% in Haiti to 100% in Sierra Leone and Zimbabwe). There was no detectable association between magnesium sulfate availability and the rate of eclampsia across sites (p = 0.12). This analysis may have been influenced by the selection of predominantly urban and peri-urban settings, and by collection of only monthly data on availability of magnesium sulfate, and is limited by the lack of demographic data in the population of women delivering in the trial areas.

CONCLUSIONS:
The large variation in eclampsia and maternal and neonatal fatality from hypertensive disorders of pregnancy between countries emphasises that inequality and inequity persist in healthcare for women with hypertensive disorders of pregnancy. Alongside the growing interest in improving community detection and health education for these disorders, efforts to improve quality of care within healthcare facilities are key. Strategies to prevent eclampsia should be informed by local data.

Cochrane Database Syst Rev. 2018 Dec 19;12:CD011689. doi: 10.1002/14651858.CD011689.pub3. (Open access available)

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis.

Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, Williams MJ, Diaz V, Pasquale J, Chamillard M, Widmer M, Tunçalp Ö, Hofmeyr GJ, Althabe F, Gülmezoglu AM, Vogel JP, Oladapo OT, Coomarasamy A.
UK

BACKGROUND:
Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide. Prophylactic uterotonic agents can prevent PPH, and are routinely recommended. The current World Health Organization (WHO) recommendation for preventing PPH is 10 IU (international units) of intramuscular or intravenous oxytocin. There are several uterotonic agents for preventing PPH but there is still uncertainty about which agent is most effective with the least side effects. This is an update of a Cochrane Review which was first published in April 2018 and was updated to incorporate results from a recent large WHO trial.

OBJECTIVES:
To identify the most effective uterotonic agent(s) to prevent PPH with the least side effects, and generate a ranking according to their effectiveness and side-effect profile.

SEARCH METHODS:
We searched the Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (24 May 2018), and reference lists of retrieved studies.

SELECTION CRITERIA:

All randomised controlled trials or cluster-randomised trials comparing the effectiveness and side effects of uterotonic agents with other uterotonic agents, placebo or no treatment for preventing PPH were eligible for inclusion. Quasi-randomised trials were excluded. Randomised trials published only as abstracts were eligible if sufficient information could be retrieved.

DATA COLLECTION AND ANALYSIS:
At least three review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We estimated the relative effects and rankings for preventing PPH ≥ 500 mL and PPH ≥ 1000 mL as primary outcomes. Secondary outcomes included blood loss and related outcomes, morbidity outcomes, maternal well-being and satisfaction and side effects. Primary outcomes were also reported for pre-specified subgroups, stratifying by mode of birth, prior risk of PPH, healthcare setting, dosage, regimen and route of administration. We performed pairwise meta-analyses and network meta-analysis to determine the relative effects and rankings of all available agents.

MAIN RESULTS:
The network meta-analysis included 196 trials (135,559 women) involving seven uterotonic agents and placebo or no treatment, conducted across 53 countries (including high-, middle- and low-income countries). Most trials were performed in a hospital setting (187/196, 95.4%) with women undergoing a vaginal birth (71.5%, 140/196).Relative effects from the network meta-analysis suggested that all agents were effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment. The three highest ranked uterotonic agents for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, misoprostol plus oxytocin combination and carbetocin. There is evidence that ergometrine plus oxytocin (RR 0.70, 95% CI 0.59 to 0.84, moderate certainty), carbetocin (RR 0.72, 95% CI 0.56 to 0.93, moderate certainty) and misoprostol plus oxytocin (RR 0.70, 95% CI 0.58 to 0.86, low certainty) may reduce PPH ≥ 500 mL compared with oxytocin. Low-certainty evidence suggests that misoprostol, injectable prostaglandins, and ergometrine may make little or no difference to this outcome compared with oxytocin.All agents except ergometrine and injectable prostaglandins were effective for preventing PPH ≥ 1000 mL when compared with placebo or no treatment. High-certainty evidence suggests that ergometrine plus oxytocin (RR 0.83, 95% CI 0.66 to 1.03) and misoprostol plus oxytocin (RR 0.88, 95% CI 0.70 to 1.11) make little or no difference in the outcome of PPH ≥ 1000 mL compared with oxytocin. Low-certainty evidence suggests that ergometrine may make little or no difference to this outcome compared with oxytocin meanwhile the evidence on carbetocin was of very low certainty. High-certainty evidence suggests that misoprostol is less effective in preventing PPH ≥ 1000 mL when compared with oxytocin (RR 1.19, 95% CI 1.01 to 1.42). Despite the comparable relative treatment effects between all uterotonics (except misoprostol) and oxytocin, ergometrine plus oxytocin, misoprostol plus oxytocin combinations and carbetocin were the highest ranked agents for PPH ≥ 1000 mL.Misoprostol plus oxytocin reduces the use of additional uterotonics (RR 0.56, 95% CI 0.42 to 0.73, high certainty) and probably also reduces the risk of blood transfusion (RR 0.51, 95% CI 0.37 to 0.70, moderate certainty) when compared with oxytocin. Carbetocin, injectable prostaglandins and ergometrine plus oxytocin may also reduce the use of additional uterotonics but the certainty of the evidence is low. No meaningful differences could be detected between all agents for maternal deaths or severe morbidity as these outcomes were rare in the included randomised trials where

they were reported.The two combination regimens were associated with important side effects. When compared with oxytocin, misoprostol plus oxytocin combination increases the likelihood of vomiting (RR 2.11, 95% CI 1.39 to 3.18, high certainty) and fever (RR 3.14, 95% CI 2.20 to 4.49, moderate certainty). Ergometrine plus oxytocin increases the likelihood of vomiting (RR 2.93, 95% CI 2.08 to 4.13, moderate certainty) and may make little or no difference to the risk of hypertension, however absolute effects varied considerably and the certainty of the evidence was low for this outcome.Subgroup analyses did not reveal important subgroup differences by mode of birth (caesarean versus vaginal birth), setting (hospital versus community), risk of PPH (high versus low risk for PPH), dose of misoprostol (≥ 600 mcg versus < 600 mcg) and regimen of oxytocin (bolus versus bolus plus infusion versus infusion only).

AUTHORS' CONCLUSIONS:
All agents were generally effective for preventing PPH when compared with placebo or no treatment. Ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination may have some additional desirable effects compared with the current standard oxytocin. The two combination regimens, however, are associated with significant side effects. Carbetocin may be more effective than oxytocin for some outcomes without an increase in side effects.

BMC Pregnancy Childbirth. 2019 Jan 18;19(1):38. doi: 10.1186/s12884-019-2181-2. (Open access available)

Intramuscular injection, intravenous infusion, and intravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage: a three-arm randomized control trial.

Charles D, Anger H, Dabash R, Darwish E, Ramadan MC, Mansy A, Salem Y, Dzuba IG, Byrne ME, Breebaart M, Winikoff B.
USA, Egypt

BACKGROUND:
Oxytocin for postpartum hemorrhage (PPH) prophylaxis is commonly administered by either intramuscular (IM) injection or intravenous (IV) infusion with both routes recommended equally and little discussion of potential differences between the two. **This trial assesses the effectiveness and safety of 10 IU oxytocin administered as IM injection versus IV infusion and IV bolus during the third stage of labor for PPH prophylaxis.**

METHODS:
In two tertiary level Egyptian maternity hospitals, women delivering vaginally without exposure to pre-delivery uterotonics were randomized to one of three prophylactic oxytocin administration groups after delivery of the baby. Blood loss was measured 1 h after delivery, and side effects were recorded. Primary outcomes were mean postpartum blood loss and proportion of women with postpartum blood loss ≥500 ml in this open-label, three-arm, parallel, randomized controlled trial.

RESULTS:
Four thousand nine hundred thirteen eligible, consenting women were randomized. Compared to IM injection, mean blood loss was 5.9% less in the IV infusion arm (95% CI: -8.5, - 3.3) and 11.1% less in the IV bolus arm (95% CI: -14.7, - 7.8). Risk of postpartum blood loss ≥500 ml in the IV infusion arm was significantly less compared to IM injection (0.8% vs. 1.5%, RR = 0.50, 95% CI: 0.27, 0.91). No side effects were reported in any arm.

CONCLUSIONS:
Intravenous oxytocin is more effective than intramuscular injection for the prevention of PPH in the third stage of labor. Oxytocin delivered by IV bolus presents no safety concerns after vaginal delivery and should be considered a safe option for PPH prophylaxis.

TRIAL REGISTRATION:
clinicaltrials.gov # NCT01914419 , posted August 2, 2013.

KEYWORDS:
Bolus oxytocin; Intramuscular oxytocin; Intravenous oxytocin; Oxytocic; Oxytocin; Oxytocin prophylaxis; Postpartum blood loss; Postpartum hemorrhage; Route of administration; Third stage of labor

PLoS One. 2018 Dec 17;13(12):e0207909. doi: 10.1371/journal.pone.0207909. eCollection 2018. (Open access available)

Peer-assisted learning after onsite, low-dose, high-frequency training and practice on simulators to prevent and treat postpartum hemorrhage and neonatal asphyxia: A pragmatic trial in 12 districts in Uganda.

Evans CL, Bazant E, Atukunda I, Williams E, Niermeyer S, Hiner C, Zahn R, Namugerwa R, Mbonye A, Mohan D.
USA, Uganda

Abstract
An urgent need exists to improve and maintain intrapartum skills of providers in sub-Saharan Africa. Peer-assisted learning may address this need, but few rigorous evaluations have been conducted in real-world settings. **A pragmatic, cluster-randomized trial in 12 Ugandan districts provided facility-based, team training for prevention and management of postpartum hemorrhage and birth asphyxia at 125 facilities.** Three approaches to facilitating simulation-based, peer assisted learning were compared. The primary outcome was the proportion of births with uterotonic given within one minute of birth. Outcomes were evaluated using observation of birth and supplemented by skills assessments and service delivery data. Individual and composite variables were compared across groups, using generalized linear models. Overall, 107, 195, and 199 providers were observed at three time points during 1,716 births across 44 facilities. Uterotonic coverage within one minute increased from: full group: 8% (CI 4%–12%) to 50% (CI 42%–59%); partial group: 19% (CI 9%–30%) to 42% (CI 31%–53%); and control group: 11% (5%–7%) to 51% (40%–61%). Observed care of mother and newborn improved in all groups. Simulated skills

maintenance for postpartum hemorrhage prophylaxis remained high across groups 7 to 8 months after the intervention. Simulated skills for newborn bag-and-mask ventilation remained high only in the full group. For all groups combined, incidence of postpartum hemorrhage and retained placenta declined 17% and 47%, respectively, from during the intervention period compared to the 6–9 month period after the intervention. Fresh stillbirths and newborn deaths before discharge decreased by 34% and 62%, respectively, from baseline to after completion, and remained reduced 6–9 months post-implementation. Significant improvements in uterotonic coverage remained across groups 6 months after the intervention. **Findings suggest that while short, simulation-based training at the facility improves care and is feasible, more complex clinical skills used infrequently such as newborn resuscitation may require more practice to maintain skills.**

PloS One. 2018 Dec 26;13(12):e0208885. doi: 10.1371/journal.pone.0208885. eCollection 2018. (Open access available)

Associations between birth kit use and maternal and neonatal health outcomes in rural Jigawa state, Nigeria: A secondary analysis of data from a cluster randomized controlled trial.

Leight J, Sharma V, Brown W, Costica L, Abdulaziz Sule F, Bjorkman Nyqvist M.
USA, Nigeria, Sweden

BACKGROUND:
The burden of maternal and neonatal mortality remains persistently high in Nigeria. Sepsis contributes significantly to both maternal and newborn mortality, and safe delivery kits have long been promoted as a cost-effective intervention to ensure hygienic delivery practices and reduce sepsis. **However, there is limited evidence on the effectiveness of home birth kit distribution by community health workers, and particularly the impact of this intervention on health outcomes.** This paper reports a secondary analysis of data from a cluster randomized trial in rural northern Nigeria in which birth kits were distributed by community health workers to pregnant women in their homes, analyzing non-experimental variation in receipt and use of birth kits. More specifically, associations between pregnant women's baseline characteristics and receipt and use of birth kits, and associations between birth kit use, care utilization and maternal and newborn outcomes were assessed.

METHODS AND FINDINGS:
Baseline, post-birth and endline data related to 3,317 births observed over a period of three years in 72 intervention communities in Jigawa state, Nigeria, were analyzed using hierarchical, logistic regression models. In total, 140 women received birth kits, and 72 women used the kits. There were no associations between baseline demographic characteristics, health history, and knowledge and attitudes and receipt of a kit, suggesting that community health workers did not systematically target the distribution of birth kits. However, women who used the kit reported reduced odds of past pregnancy complications (OR = 0.44, 95% CI: 0.19-1.00) as well as significantly higher odds of feeling generally healthy at baseline (OR = 2.00, 95% CI: 1.06-3.76), of exposure to radio media (OR = 1.97, 95% CI: 1.21-

3.22), and of perceiving themselves as having a low-risk pregnancy (OR = 3.05, 95% CI:1.39-6.68). While there were no significant associations between birth kit use and facility based delivery, skilled birth attendance or post-natal care, women who used a kit exhibited significantly lower odds of completing four or more ANC visits (adjusted OR = 0.39, 95% CI: 0.18-0.85) and significantly higher odds of reporting prolonged labor (adjusted OR = 4.75, 95% CI: 1.36-16.59), and post-partum bleeding (adjusted OR = 3.25, 95% CI: 1.11-9.52).

CONCLUSIONS:
This evidence suggests that use of birth kits is low in a rural population characterized by minimal baseline utilization of maternal and neonatal health services, and the use of birth kits was not associated with reductions in maternal or neonatal morbidity. While further research is required to understand how the effectiveness of birth kits may be shaped by the mechanism through which women access and utilize the kits, our findings suggest that the provision of kits to women outside of the formal health system may be associated with increased risk of adverse outcomes.

Maternal nutrition and micronutrient supplementation

Am J Clin Nutr. 2019 Feb 1;109(2):457-469. doi: 10.1093/ajcn/nqy228. (Open access available)

A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the Women First trial.

Hambidge KM, Westcott JE, Garcés A, Figueroa L, Goudar SS, Dhaded SM, Pasha O, Ali SA, Tshefu A, Lokangaka A, Derman RJ, Goldenberg RL, Bose CL, Bauserman M, Koso-Thomas M, Thorsten VR, Sridhar A, Stolka K, Das A, McClure EM, Krebs NF; Women First Preconception Trial Study Group.
Guatemala, India, Pakistan, USA, Democratic Republic of the Congo

Background:
Reported benefits of maternal nutrition supplements commenced during pregnancy in low-resource populations have typically been quite limited.

Objectives:
This study tested the effects on newborn size, especially length, of commencing nutrition supplements for women in low-resource populations ≥3 mo before conception (Arm 1), compared with the same supplement commenced late in the first trimester of pregnancy (Arm 2) or not at all (control Arm 3).

Methods:
Women First was a 3-arm individualized randomized controlled trial (RCT). The intervention was a lipid-based micronutrient supplement; a protein-energy supplement was also provided if maternal body mass index (kg/m2) was <20 or gestational weight gain was less

than recommendations. Study sites were in rural locations of the Democratic Republic of the Congo (DRC), Guatemala, India, and Pakistan. The primary outcome was length-for-age z score (LAZ), with all anthropometry obtained <48 h post delivery. Because gestational ages were unavailable in DRC, outcomes were determined for all 4 sites from WHO newborn standards (non-gestational-age-adjusted, NGAA) as well as INTERGROWTH-21st fetal standards (3 sites, gestational age-adjusted, GAA).

Results:
A total of 7387 nonpregnant women were randomly assigned, yielding 2451 births with NGAA primary outcomes and 1465 with GAA outcomes. Mean LAZ and other outcomes did not differ between Arm 1 and Arm 2 using either NGAA or GAA. Mean LAZ (NGAA) for Arm 1 was greater than for Arm 3 (effect size: +0.19; 95% CI: 0.08, 0.30, P = 0.0008). For GAA outcomes, rates of stunting and small-for-gestational-age were lower in Arm 1 than in Arm 3 (RR: 0.69; 95% CI: 0.49, 0.98, P = 0.0361 and RR: 0.78; 95% CI: 0.70, 0.88, P < 0.001, respectively). Rates of preterm birth did not differ among arms.

Conclusions:
In low-resource populations, benefits on fetal growth-related birth outcomes were derived from nutrition supplements commenced before conception or late in the first trimester. This trial was registered at clinicaltrials.gov as NCT01883193.

BMC Pregnancy Childbirth. 2018 Jul 4;18(1):286. doi: 10.1186/s12884-018-1915-x. (Open access available)

A village-matched evaluation of providing a local supplemental food during pregnancy in rural Bangladesh: a preliminary study.

Stevens B, Watt K, Brimbecombe J, Clough A, Judd JA, Lindsay D.
Australia

BACKGROUND:
Prenatal balanced protein energy supplementation consumed by undernourished women improves mid-upper arm circumference in early infancy. This study aimed to identify whether locally produced maternal food-based supplementation improved anthropometric measures at birth and early infancy.

METHODS:
A village-matched evaluation, applying principles of a cluster randomised controlled trial, of a locally produced supplemental food to 87 undernourished pregnant women. 12 villages (intervention: n = 8; control: n = 4) in Pirganj sub-district, Rangpur District, northern Bangladesh. Daily supplements were provided.

RESULTS:
Anthropometric data at birth were available for 77 mother-infant dyads and longer-term infant growth data for 75 infants. Mid-upper arm circumference (MUAC) was significantly larger in infants of mothers in the intervention group compared with the control group at

6 months (p < 0.05). The mean birth weight in babies of supplemented mothers (mean: 2·91 kg; SD: 0·19) was higher than in babies of mothers in the control group (mean: 2·72 kg; SD: 0·13), and these changes persisted until 6 months. Also, the proportion of low birth weight babies in the intervention group was much lower (event rate = 0.04) than in the control group (event rate = 0.16). However, none of these differences were statistically significant (p > 0·05; most likely due to small sample size). The intervention reduced the risk of wasting at 6 months by 63.38% (RRR = 0.6338), and of low birth weight by 88·58% (RRR = 0.8858), with NNT of 2.22 and 6.32, respectively. Only three pregnant women require this intervention in order to prevent wasting at 6 months in one child, and seven need the intervention to prevent low birth weight of one child.

CONCLUSIONS:
Locally produced food-based balanced protein energy supplementation in undernourished pregnant women in northern Bangladesh resulted in larger MUAC in infants at 6 months. Further research, with larger sample sizes, is required to confirm the role of locally produced supplementation for undernourished pregnant women on weight and linear growth in newborns and infants.

Comment
No Bangladeshi researcher named as an author.

Matern Child Health J. 2019 Feb;23(2):258-264. doi: 10.1007/s10995-018-2648-1.

Effects of Food Supplementation During Pregnancy on Maternal Weight Gain, Hemoglobin Levels and Pregnancy Outcomes in Iran.

Tabrizi JS, Asghari A, Pourali F, Kousha H, Nikniaz L.
Iran

Abstract
Objectives In this study, the effects of food supplementation during pregnancy on maternal weight gain, hemoglobin (Hb) levels, and pregnancy outcomes were evaluated. Methods In this randomized controlled trial, we **recruited 1360 pregnant women with a gestational age of 10 weeks who had BMI < 18.5 and hemoglobin < 10.5/dL from rural areas of the east Azerbaijan province in Iran. Rural areas were randomly assigned into two groups: food-supplemented and control areas. In food-supplemented areas the food supplement was provided (1500 kcal/d) from 10 weeks of pregnancy through to the end.** Information on demographic data were collected and anthropometric and Hb measurements were taken using standard instruments. Results **The average weight gain was 9.1 ± 1.8 kg and 7.9 ± 1.6 kg in supplemented and control groups respectively, which was significantly different (p = 0.001).** Also, a significant time × treatment interaction in maternal average weight gain (p = 0.001) was observed. The mean Hb decreased from 12 mg/dl and 12.1 mg/dl in week 10 to 11.9 mg/dl and 11.7 mg/dl in week 20 in the supplemented and control groups respectively, which was significant only for the control group. Between-group comparisons revealed significant differences in the rates of low birth weight (LBW) infants (p = 0.001) and preterm births (p = 0.013). Conclusion for

practice Food supplementation significantly reduced the prevalence of poor maternal weight gain, infants with low birth weight, and preterm births compared to no intervention.

Matern Child Health J. 2019 Feb;23(2):155-163. doi: 10.1007/s10995-018-2605-z.

Effect of Maternal Vitamin B12 Supplementation on Cognitive Outcomes in South Indian Children: A Randomized Controlled Clinical Trial.

Thomas S, Thomas T, Bosch RJ, Ramthal A, Bellinger DC, Kurpad AV, Duggan CP, Srinivasan K.
India, USA

Abstract
Objectives To examine the effects of oral maternal vitamin B12 supplementation during pregnancy and early lactation on cognitive development in children. Method **We studied 218 children born to mothers enrolled in a placebo-controlled, randomized trial of vitamin B12 supplementation during pregnancy through 6 weeks post-partum.** Cognitive functions were assessed at 30 months using the Bayley Scales of Infant Development- 3rd edition (BSID III). The association of maternal sociodemographic characteristics, maternal biochemical status during pregnancy, birth weight and home environment with each sub-domain of BSID-III was examined using linear regression analysis. Separate multiple linear regression analyses for each of the BSID-III sub-domains with maternal trimester specific nutritional biomarker status was conducted. Results **Children of mothers who received oral vitamin B12 supplementation had significantly higher scores on expressive language compared to children of mothers who received placebo (β = 0.14, P = 0.03).** Children of mothers with elevated serum total homocysteine (tHcy) in the second and third trimesters of pregnancy had significantly lower scores on expressive language (β = - 0.18, P = 0.03 and β = - 0.19, P = 0.02, respectively) and gross motor domains (β = - 0.23, P = 0.008 and β = - 0.30, P = 0.001, respectively) of BSID-III adjusted for treatment arm and multiple confounders, compared with children whose mothers did not have elevated tHcy. Conclusions for practice **Maternal B12 supplementation during pregnancy was associated with higher expressive language scores in children at 30 months.** Elevated maternal tHcy levels during pregnancy had negative associations with expressive language and gross motor domains of BSID-III. Larger trials of maternal B12 supplementation are needed to confirm these findings.

PLoS One. 2018 Oct 11;13(10):e0201038. doi: 10.1371/journal.pone.0201038. eCollection 2018. (Open access available)

Pre- and post-natal macronutrient supplementation for HIV-positive women in Tanzania: Effects on infant birth weight and HIV transmission.

Magohe A, Mackenzie T, Kimario J, Lukmanji Z, Hendricks K, Koethe J, Neke NM, Tvaroha S, Connor R, Waddell R, Maro I, Matee M, Pallangyo K, Bakari M, von Reyn CF; DarDar-2 Study Team.

Tanzania, USA, Japan

Abstract
OBJECTIVE:
To determine if a protein-calorie supplement (PCS) plus a micronutrient supplement (MNS) improves outcomes for HIV-infected lactating women and their infants.

DESIGN:
Randomized, controlled trial.

SETTING:
Dar es Salaam, Tanzania.

SUBJECTS, PARTICIPANTS:
Pregnant HIV-infected women enrolled in PMTCT programs who intended to breastfeed for 6 months.

INTERVENTION:
Randomization 1:1 to administration of a PCS plus MNS versus MNS alone among 96 eligible women beginning in the third trimester and continuing for 6 months of breast-feeding.

MAIN OUTCOME MEASURE(S):
Primary: infant weight at 3 months. Secondary: maternal BMI at 6 months.

RESULTS:
PCS resulted in significant increases in daily energy intake compared to MNS at all time points (range of differences: +388-719 Kcal); and increases in daily protein intake (range of differences: +22-33 gm). Infant birth weight (excluding twins) was higher in the PCS than MNS groups: 3.30 kg vs 3.04 kg (p = 0.04). Infant weight at 3 months did not differ between PCS and MNS groups: 5.63 kg vs 5.99 kg (p = 0.07). Maternal BMI at 6 months did not differ between PCS and MNS groups: 24.3 vs 23.8 kg/m2 (p = 0.68). HIV transmission occurred in 0 infants in the PCS group vs 4 in the MNS group (p = 0.03).

CONCLUSIONS:
In comparison to MNS the PCS + MNS intervention was well tolerated, increased maternal energy and protein intake, and increased infant birth weight, but not weight at 3 months or maternal BMI at 6 months. Reduced infant HIV transmission in the PCS + MNS group was observed.

Lancet. 2019 Jan 26;393(10169):330-339. doi: 10.1016/S0140-6736(18)31818-X. (Open access available)

Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial.

Hofmeyr GJ, Betrán AP, Singata-Madliki M, Cormick G, Munjanja SP, Fawcus S, Mose S, Hall D, Ciganda A, Seuc AH, Lawrie TA, Bergel E, Roberts JM, von Dadelszen P, Belizán JM; Calcium and Pre-eclampsia Study Group.
South Africa, WHO, Switzerland, Zimbabwe, Argentina, USA, UK

BACKGROUND:
Reducing deaths from hypertensive disorders of pregnancy is a global priority. Low dietary calcium might account for the high prevalence of pre-eclampsia and eclampsia in low-income countries. Calcium supplementation in the second half of pregnancy is known to reduce the serious consequences of pre-eclampsia; however, the effect of calcium supplementation during placentation is not known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks' gestation) prevents the development of pre-eclampsia METHODS: **We did a multicountry, parallel arm, double-blind, randomised, placebo-controlled trial in South Africa, Zimbabwe, and Argentina.** Participants with previous pre-eclampsia and eclampsia received 500 mg calcium or placebo daily from enrolment prepregnancy until 20 weeks' gestation. Participants were parous women whose most recent pregnancy had been complicated by pre-eclampsia or eclampsia and who were intending to become pregnant. All participants received unblinded calcium 1·5 g daily after 20 weeks' gestation. The allocation sequence (1:1 ratio) used computer-generated random numbers in balanced blocks of variable size. The primary outcome was pre-eclampsia, defined as gestational hypertension and proteinuria. The trial is registered with the Pan-African Clinical Trials Registry, number PACTR201105000267371. The trial closed on Oct 31, 2017.

FINDINGS:
Between July 12, 2011, and Sept 8, 2016, we randomly allocated 1355 women to receive calcium or placebo; 331 of 678 participants in the calcium group versus 320 of 677 in the placebo group became pregnant, and 298 of 678 versus 283 of 677 had pregnancies beyond 20 weeks' gestation**. Pre-eclampsia occurred in 69 (23%) of 296 participants in the calcium group versus 82 (29%) of 283 participants in the placebo group with pregnancies beyond 20 weeks' gestation (risk ratio [RR] 0·80, 95% CI 0·61-1·06; p=0·121).** For participants with compliance of more than 80% from the last visit before pregnancy to 20 weeks' gestation, the pre-eclampsia risk was 30 (21%) of 144 versus 47 (32%) of 149 (RR 0·66, CI 0·44-0·98; p=0·037). There were no serious adverse effects of calcium reported.

INTERPRETATION:
Calcium supplementation that commenced before pregnancy until 20 weeks' gestation, compared with placebo, did not show a significant reduction in recurrent pre-eclampsia. As the trial was powered to detect a large effect size, we cannot rule out a small to moderate effect of this intervention.

J Nutr. 2019 Apr 22. pii: nxz046. doi: 10.1093/jn/nxz046. [Epub ahead of print] (Open access available)

Antenatal Multiple Micronutrient Supplementation Compared to Iron-Folic Acid Affects Micronutrient Status but Does Not Eliminate Deficiencies in a Randomized Controlled Trial among Pregnant Womenof Rural Bangladesh.

Schulze KJ, Mehra S, Shaikh S, Ali H, Shamim AA, Wu LS, Mitra M, Arguello MA, Kmush B, Sungpuag P, Udomkesmelee E, Merrill R, Klemm RDW, Ullah B, Labrique AB, West KP, Christian P.
Bangladesh

BACKGROUND:
Antenatal multiple micronutrient (MM) supplementation improves birth outcomes relative to iron-folic acid (IFA) in developing countries, but limited data exist on its impact on pregnancy micronutrient status.

OBJECTIVE:
We assessed the efficacy of a daily MM (15 nutrients) compared with IFA supplement, each providing approximately 1 RDA of nutrients and given beginning at pregnancy ascertainment, on late pregnancy micronutrient status of women in rural Bangladesh. Secondarily, we explored other contributors to pregnancy micronutrient status.

METHODS:
Within a double-masked trial (JiVitA-3) among 44,500 pregnant women, micronutrient status indicators were assessed in n = 1526 women, allocated by cluster to receive daily MM (n = 749) or IFA (n = 777), at 10 wk (baseline: before supplementation) and 32 wk (during supplementation) gestation. Efficacy of MM supplementation on micronutrient status indicators at 32 wk was assessed, controlling for baseline status and other covariates (e.g., inflammation and season), in regression models.

RESULTS:
Baseline status was comparable by intervention. Prevalence of deficiency among all participants was as follows: anemia, 20.6%; iron by ferritin, 4.0%; iron by transferrin receptor, 4.7%; folate, 2.5%; vitamin B-12, 35.4%; vitamin A, 6.7%; vitamin E, 57.7%; vitamin D, 64.0%; zinc, 13.4%; and iodine, 2.6%. At 32 wk gestation, vitamin B-12, A, and D and zinc status indicators were 3.7-13.7% higher, and ferritin, γ-tocopherol, and thyroglobulin indicators were 8.7-16.6% lower, for the MM group compared with the IFA group, with a 15-38% lower prevalence of deficiencies of vitamins B-12, A, and D and zinc (all $P < 0.05$). However, indicators typically suggested worsening status during pregnancy, even with supplementation, and baseline status or other covariates were more strongly associated with late pregnancy indicators than was MM supplementation.

CONCLUSIONS:
Rural Bangladeshi women commonly entered pregnancy deficient in micronutrients other than iron and folic acid. Supplementation with MM improved micronutrient status, although deficiencies persisted. Preconception supplementation or higher nutrient doses may be warranted to support nutritional demands of pregnancy in undernourished populations.

BMC Pregnancy Childbirth. 2019 Feb 4;19(1):54. doi: 10.1186/s12884-019-2200-3. (Open access available)

Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial.

Jose A, Mahey R, Sharma JB, Bhatla N, Saxena R, Kalaivani M, Kriplani A.
India

Abstract
BACKGROUND:
To evaluate the efficacy and safety of intravenous Ferric Carboxymaltose. (FCM) in comparison with intravenous Iron sucrose complex (ISC) for treatment of iron deficiency anemia in pregnancy.

METHODS:
A randomized clinical trial was conducted from (January 2016-August 2017). at a tertiary hospital. Pregnant women diagnosed with moderate to severe iron deficiency anaemia were screened for the study. One hundred patients were randomized to receive either intravenous FCM or ISC. Primary outcome was rise in hemoglobin (Hb) from baseline after 12 weeks. Secondary outcomes were change in RBC indices, serum iron studies, improvement in fatigue scores, number of visits and perinatal outcome.

RESULTS:
Mean rise in Hb at 12 weeks was significantly higher in FCM group (29 g/L vs 22 g/L; p value < 0.01). FCM was associated with greater improvement in fatigue scores. Number of visits were significantly less in FCM group. No serious adverse events were noted in either group.

CONCLUSION:
Treatment with FCM resulted in rapid replenishment of iron stores in pregnant women with significantly higher Hb rise over a 12 week period. The convenient dosing with lesser number of total doses to complete the treatment will lead to better compliance in community setting.

Cochrane Database Syst Rev. 2019 Mar 14;3:CD004905. doi: 10.1002/14651858.CD004905.pub6. (Open access available)b

Multiple-micronutrient supplementation for women during pregnancy.

Keats EC, Haider BA, Tam E, Bhutta ZA.

BACKGROUND:
Multiple-micronutrient (MMN) deficiencies often coexist among women of reproductive age in low- and middle-income countries. They are exacerbated in pregnancy due to the

increased demands of the developing fetus, leading to potentially adverse effects on the mother and baby. A consensus is yet to be reached regarding the replacement of iron and folic acid supplementation with MMNs. Since the last update of this Cochrane Review in 2017, evidence from several trials has become available. The findings of this review will be critical to inform policy on micronutrient supplementation in pregnancy.

OBJECTIVES:
To evaluate the benefits of oral multiple-micronutrient supplementation during pregnancy on maternal, fetal and infant health outcomes.

SEARCH METHODS:
For this 2018 update, on 23 February 2018 we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of retrieved studies. We also contacted experts in the field for additional and ongoing trials.

SELECTION CRITERIA:
All prospective randomised controlled trials evaluating MMN supplementation with iron and folic acid during pregnancy and its effects on pregnancy outcomes were eligible, irrespective of language or the publication status of the trials. We included cluster-randomised trials, but excluded quasi-randomised trials. Trial reports that were published as abstracts were eligible.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We assessed the quality of the evidence using the GRADE approach.

MAIN RESULTS:
We identified 21 trials (involving 142,496 women) as eligible for inclusion in this review, but only 20 trials (involving 141,849 women) contributed data. Of these 20 trials, 19 were conducted in low- and middle-income countries and compared MMN supplements with iron and folic acid to iron, with or without folic acid. One trial conducted in the UK compared MMN supplementation with placebo. In total, eight trials were cluster-randomised.MMN with iron and folic acid versus iron, with or without folic acid (19 trials)MMN supplementation probably led to a slight reduction in preterm births (average risk ratio (RR) 0.95, 95% confidence interval (CI) 0.90 to 1.01; 18 trials, 91,425 participants; moderate-quality evidence), and babies considered small-for-gestational age (SGA) (average RR 0.92, 95% CI 0.88 to 0.97; 17 trials; 57,348 participants; moderate-quality evidence), though the CI for the pooled effect for preterm births just crossed the line of no effect. **MMN reduced the number of newborn infants identified as low birthweight (LBW) (average RR 0.88, 95% CI 0.85 to 0.91; 18 trials, 68,801 participants; high-quality evidence).** We did not observe any differences between groups for perinatal mortality (average RR 1.00, 95% CI 0.90 to 1.11; 15 trials, 63,922 participants; high-quality evidence). MMN supplementation led to slightly fewer stillbirths (average RR 0.95, 95% CI 0.86 to 1.04; 17 trials, 97,927 participants; high-quality evidence) but, again, the CI for the pooled effect just crossed the line of no effect. MMN supplementation did not have an important effect on neonatal mortality (average RR 1.00,

95% CI 0.89 to 1.12; 14 trials, 80,964 participants; high-quality evidence). We observed little or no difference between groups for the other maternal and pregnancy outcomes: maternal anaemia in the third trimester (average RR 1.04, 95% CI 0.94 to 1.15; 9 trials, 5912 participants), maternal mortality (average RR 1.06, 95% CI 0.72 to 1.54; 6 trials, 106,275 participants), miscarriage (average RR 0.99, 95% CI 0.94 to 1.04; 12 trials, 100,565 participants), delivery via a caesarean section (average RR 1.13, 95% CI 0.99 to 1.29; 5 trials, 12,836 participants), and congenital anomalies (average RR 1.34, 95% CI 0.25 to 7.12; 2 trials, 1958 participants). **However, MMN supplementation probably led to a reduction in very preterm births (average RR 0.81, 95% CI 0.71 to 0.93; 4 trials, 37,701 participants).** We were unable to assess a number of prespecified, clinically important outcomes due to insufficient or non-available data.When we assessed primary outcomes according to GRADE criteria, the quality of evidence for the review overall was moderate to high. We graded the following outcomes as high quality: LBW, perinatal mortality, stillbirth, and neonatal mortality. The outcomes of preterm birth and SGA we graded as moderate quality; both were downgraded for funnel plot asymmetry, indicating possible publication bias.We carried out sensitivity analyses excluding trials with high levels of sample attrition (> 20%). We found that results were consistent with the main analyses for all outcomes. We explored heterogeneity through subgroup analyses by maternal height, maternal body mass index (BMI), timing of supplementation, dose of iron, and MMN supplement formulation (UNIMMAP versus non-UNIMMAP). There was a greater reduction in preterm births for women with low BMI and among those who took non-UNIMMAP supplements. We also observed subgroup differences for maternal BMI and maternal height for SGA, indicating greater impact among women with greater BMI and height. Though we found that MMN supplementation made little or no difference to perinatal mortality, the analysis demonstrated substantial statistical heterogeneity. We explored this heterogeneity using subgroup analysis and found differences for timing of supplementation, whereby higher impact was observed with later initiation of supplementation. For all other subgroup analyses, the findings were inconclusive. MMN versus placebo (1 trial)A single trial in the UK found little or no important effect of MMN supplementation on preterm births, SGA, or LBW but did find a reduction in maternal anaemia in the third trimester (RR 0.66, 95% CI 0.51 to 0.85), when compared to placebo. This trial did not measure our other outcomes.

AUTHORS' CONCLUSIONS:
Our findings suggest a positive impact of MMN supplementation with iron and folic acid on several birth outcomes. MMN supplementation in pregnancy led to a reduction in babies considered LBW, and probably led to a reduction in babies considered SGA. **In addition, MMN probably reduced preterm births. No important benefits or harms of MMN supplementation were found for mortality outcomes (stillbirths, perinatal and neonatal mortality).** These findings may provide some basis to guide the replacement of iron and folic acid supplements with MMN supplements for pregnant women residing in low- and middle-income countries.

J Family Med Prim Care. 2019 Feb;8(2):378-384. doi: 10.4103/jfmpc.jfmpc_339_18. (Open access available)

Effect of iron and folic acid tablet versus capsule formulation on treatment compliance and iron status among pregnant women: A randomized controlled trial.

Srivastava R, Kant S, Singh AK, Saxena R, Yadav K, Pandav CS.
India

Abstract
BACKGROUND:
Iron supplementation during pregnancy in programmatic settings has failed to produce desired results. Formulation of iron supplementation may have a role in compliance and hematological parameters.

OBJECTIVE:
We did this study to compare the compliance to iron supplementation, change in mean hemoglobin and serum ferritin level after iron supplementation in capsule form and tablet form during pregnancy.

MATERIALS AND METHODS:
In this single-blinded (investigator blinded), active comparator, randomized controlled trial we enrolled pregnant women (aged ≥18 years) from May to November 2014 during second trimester to receive iron supplementation either as capsule (ferrous fumarate) or tablet (ferrous sulphate) during entire pregnancy. The outcome was compliance (good compliance ≥ 90%) to iron supplementation assessed by pill count and change in mean hemoglobin and serum ferritin. Statistical significance was tested using Chi-square test and Student's t test.

RESULTS:
We enrolled and randomized 204 pregnant women for iron supplementation; capsule form (*n*= 100) and tablet form (*n* = 104). Out of which 52 (25.5%) women (23 in capsule arm and 29 in tablet arm) were lost to follow up. **As compared to tablet arm, the capsule arm had higher good compliance (22% vs 16.8%), increase in mean hemoglobin (0.79 vs 0.44 gm/dL) and increase in mean serum ferritin (2.50 vs -2.14 ng/mL), but the difference was not statistically significant.**

CONCLUSION:
Pregnant women who received either of the formulation reported a low compliance. Iron supplementation in capsule formulation resulted in more increase in blood hemoglobin level, though clinically insignificant.

Endocr Connect. 2019 May 1. pii: EC-19-0123.R1. doi: 10.1530/EC-19-0123. [Epub ahead of print] (Open access available)

Prenatal vitamin D and cord blood insulin-like growth factors in Dhaka, Bangladesh.

Bilic M, Qamar H, Onoyovwi A, Korsiak J, Papp E, Al Mahmud A, Weksberg R, Gernand AD, Harrington J, Roth DE.
Bangladesh

Abstract
Fetal growth restriction is linked to adverse health outcomes and is prevalent in low- and middle-incomecountries; however, determinants of fetal growth are still poorly understood. The objectives were to determine the effect of prenatal vitamin D supplementation on the insulin-like growth factor (IGF) axis at birth, to compare concentrations of IGF-I in newborns in Bangladesh to a European reference population, and to estimate associations between IGF protein concentrations and birth size**. In a randomized controlled trial in Dhaka, Bangladesh, pregnant women enrolled at 17-24 weeks gestation were assigned to weekly oral vitamin D3 supplementation from enrolment to delivery at doses of 4200 IU/week, 16800 IU/week, 28000 IU/week or placebo.** In this sub-study, 559 woman-infant pairs were included for analysis and cord blood IGF protein concentrations were quantified at birth. **There were no significant effects of vitamin D supplementation on cord blood concentrations of IGF-I (p=0.398), IGF-II (p=0.525), binding proteins (BP) IGFBP-1 (p=0.170), IGFBP-3 (p=0.203), or the molar ratio of IGF-I/IGFBP-3 (p=0.941).** In comparison to a European reference population, 6% of girls and 23% of boys had IGF-I concentrations below the 2.5th percentile of the reference population. IGF-I, IGF-II, IGFBP-3 and the IGF-I/IGFBP-3 ratio were positively associated with at least one anthropometric parameter, whereas IGFBP-1 was negatively associated with birth anthropometry. In conclusion, prenatal vitamin D supplementation does not alter or enhance fetal IGF pathways.

Family planning and birth spacing

J Glob Health. 2018 Dec;8(2):020406. doi: 10.7189/jogh.08.020406. (Open access available)

Impact of integrating a postpartum family planning program into a community-based maternal and newborn health program on birth spacing and preterm birth in rural Bangladesh.

Baqui AH, Ahmed S, Begum N, Khanam R, Mohan D, Harrison M, Al Kabir A, McKaig C, Brandes N, Norton M, Ahmed S; Projahnmo Study Group in Bangladesh.
USA, Bangladesh

Background:
Short birth intervals are associated with an increased risk of adverse perinatal outcomes. However, reduction of rates of short birth intervals is challenging in low-resource settings where majority of the women deliver at home with limited access to family planning services immediately after delivery. This study examines the feasibility of integrating a post-partum family planning intervention package within a community-based maternal and newborn health intervention package, and evaluates the impact of integration on reduction of rates of short birth intervals and preterm births.

Methods:
In a quasi-experimental trial design, unions with an average population of about 25 000 and a first level health facility were allocated to an intervention arm (n = 4) to receive integrated post-partum family planning and maternal and newborn health (PPFP-MNH) interventions, or to a control arm (n = 4) to receive the MNH interventions only. Trained community health workers were the primary outreach service providers in both study arms. The primary outcomes of interest were birth spacing and preterm births. We also examined if there were any unintended consequences of integration.

Results:
At baseline, short birth intervals of less than 24 months and preterm birth rates were similar among women in the intervention and control arms. Integrating PPFP into the MNH intervention package did not negatively influence maternal and neonatal outcomes; during the intervention period, there was no difference in community health workers' home visit coverage or neonatal care practices between the two study arms. Compared to the control arm, women in the intervention arm had a 19% lower risk of short birth interval (adjusted relative risk (RR) = 0.81, 95% confidence interval (CI) = 0.69-0.95) and 21% lower risk of preterm birth (adjusted RR = 0.79; 95% CI = 0.63-0.99).

Conclusions:
Study findings demonstrate the feasibility and effectiveness of integrating PPFP interventions into a community based MNH intervention package. Thus, MNH programs should consider systematically integrating PPFP as a service component to improve pregnancy spacing and reduce the risk of preterm birth.

Meningitis and encephalitis

Mobile phones and Apps

Hum Resour Health. 2018 Sep 19;16(1):49. doi: 10.1186/s12960-018-0315-7. (Open access available)

The use of low-cost Android tablets to train community health workers in Mukono, Uganda, in the recognition, treatment and prevention of pneumonia in children under five: a pilot randomised controlled trial.

O'Donovan J, Kabali K, Taylor C, Chukhina M, Kading JC, Fuld J, O'Neil E.
UK, Uganda

BACKGROUND:
Since 2012, The World Health Organization and UNICEF have advocated for community health workers (CHWs) to be trained in Integrated Community Case Management (iCCM) of common childhood illnesses, such as pneumonia. Despite the effectiveness of iCCM, CHWs

face many barriers to accessing training. This pilot study compares traditional training with using locally made videos loaded onto low-cost Android tablets to train CHWs on the pneumonia component of iCCM.

METHODS:
We conducted a pilot **randomised controlled trial with CHWs in the Mukono District of Uganda.** The unit of randomisation was the sub-county level, and the unit of analysis was at the level of the individual CHW. Eligible CHWs had completed basic iCCM training but had not received any refresher training on the pneumonia component of iCCM in the preceding 2 years. CHWs in the control group received training in the recognition, treatment, and prevention of pneumonia as it is currently delivered, through a 1-day, in-person workshop. CHWs allocated to the intervention group received training via locally made educational videos hosted on low-cost Android tablets. The primary outcome was change in knowledge acquisition, assessed through a multiple choice questionnaire before and after training, and a post-training clinical assessment. The secondary outcome was a qualitative evaluation of CHW experiences of using the tablet platform.

RESULTS:
In the study, 129 CHWs were enrolled, 66 and 63 in the control and intervention groups respectively. CHWs in both groups demonstrated an improvement in multiple choice question test scores before and after training; however, there was no statistically significant difference in the improvement between groups ($t = 1.15$, $p = 0.254$). There was a statistically significant positive correlation (Pearson's $r = 0.26$, $p = 0.03$) linking years of education to improvement in test scores in the control group, which was not present in the intervention group. The majority of CHWs expressed satisfaction with the use of tablets as a training tool; however, some reported technical issues ($n = 9$).

CONCLUSION:
Tablet-based training is comparable to traditional training in terms of knowledge acquisition. It also proved to be feasible and a satisfactory means of delivering training to CHWs. Further research is required to understand the impacts of scaling such an intervention.

J Glob Health. 2018 Dec;8(2):020807. doi: 10.7189/jogh.08.020807. (Open access available)

Assessing the reactivity to mobile phones and repeated surveys on reported care-seeking for common childhood illnesses in rural India.

Nair H, Williams LJ, Marsh A, Lele P, Bhattacharjee T, Chavan U, Hirve S, Campbell H, Juvekar S.
UK, India, Ghana

Background:
Traditionally, health care-seeking for child illness is assessed through population-based and nationally representative demographic and health surveys (DHS) that are conducted once

every five to seven years and are based on maternal recall. These maternal reports are subject to recall bias. Mobile phones (with the use of GPS technology) have the potential to constantly track movements of phone owners and provide high quality and more accurate data at a population level in low and middle income countries (LMICs) to assess the validity of maternal recall. **We provided a group of mothers with smartphones installed with a location-aware application and visited them monthly to administer a survey questionnaire on care-seeking for diarrhoea, fever and cough with fever.** This paper assesses for any reactivity to smartphones or repeated study contacts for measuring care-seeking and if this resulted in change in health care provider preference.

Methods:
We enrolled 749 mothers from rural areas of Pune district in Maharashtra, India and randomly allocated them to one of three groups - a longitudinal phone group, a longitudinal control group and a cross-sectional control group. We collected baseline information from mothers, including individual and household demographic and socio-economic characteristics and care-seeking preferences for child illness. We followed up both longitudinal groups monthly and each cross-sectional sub-group once over a period of 6 months. At each follow up, we administered questions identical to those in the National Family Health Survey (NFHS) questionnaire to determine an episode of diarrhoea, fever or cough within the last 15 days, care seeking for the same, and the type of provider. The data were analysed using the χ test or Fisher Exact Test for categorical variables, or with the Kruskall-Wallis non-parametric test for continuous variables (due to the non-normal nature of the data). Multivariable joint models of group and visit time were analysed with logistic regression methods.

Results:
All three groups were similar in their socio-demographic characteristics at baseline. We did not observe any significant difference in care seeking for diarrhoea, fever or cough with fever between groups. Also, we did not observe any significant difference in proportion of children seeking care from the private sector.

Conclusions:
We did not observe any reactivity in this study due to the presence of the phone (Hawthorne effect) or repeated study visits. The study also shows the potential of using GPS enabled smartphones to enrich DHS surveys in LMICs like India. However, further studies need to be conducted in other population groups before the findings can be generalised.

JMIR Mhealth Uhealth. 2018 Nov 20;6(11):e10239. doi: 10.2196/10239. (Open access available)

Text Messages Sent to Household Tuberculosis Contacts in Kampala, Uganda: Process Evaluation.

Meyer AJ, Babirye D, Armstrong-Hough M, Mark D, Ayakaka I, Katamba A, Haberer JE, Davis JL.

USA, Uganda

BACKGROUND:
Previous studies have reported the inconsistent effectiveness of text messaging (short message service, SMS) for improving health outcomes, but few have examined to what degree the quality, or "fidelity," of implementation may explain study results.

OBJECTIVE:
The aim of this study was to determine the fidelity of a one-time text messaging (SMS) intervention to promote the uptake of tuberculosis evaluation services among household contacts of index patients with tuberculosis.

METHODS:
From February to June 2017, we nested a process evaluation of text message (SMS) delivery within the intervention arm of a randomized controlled trial of tuberculosis contact investigation in Kampala, Uganda. Because mobile service providers in Uganda do not provide delivery confirmations, we asked household tuberculosis contacts to confirm the receipt of a one-time tuberculosis-related text message (SMS) by sending a text message (SMS) reply through a toll-free "short code." Two weeks later, a research officer followed up by telephone to confirm the receipt of the one-time text message (SMS) and administer a survey. We considered participants lost to follow-up after 3 unsuccessful call attempts on 3 separate days over a 1-week period.

RESULTS:
Of 206 consecutive household contacts, 119 had a text message (SMS) initiated from the server. While 33% (39/119) were children aged 5-14 years, including 20% (24/119) girls and 13% (15/119) boys, 18 % (21/119) were adolescents or young adults, including 12% (14/119) young women and 6% (7/119) young men. 50% (59/119) were adults, including 26% (31/119) women and 24% (28/119) men. Of 107 (90%) participants for whom we could ascertain text message (SMS) receipt status, 67% (72/107) confirmed text message (SMS) receipt, including 22% (24/107) by reply text message (SMS) and 45% (48/107) during the follow-up telephone survey. No significant clinical or demographic differences were observed between those who did and did not report receiving the text message (SMS). Furthermore, 52% (56/107) reported ever reading the SMS. The cumulative likelihood of a text message (SMS) reaching its target and being read and retained by a participant was 19%.

CONCLUSIONS:
The fidelity of a one-time text message (SMS) intervention to increase the uptake of household tuberculosis contact investigation and linkage to care was extremely low, a fact only discoverable through detailed process evaluation. This study suggests the need for systematic process monitoring and reporting of implementation fidelity in both research studies and programmatic interventions using mobile communications to improve health.

ar J. 2018 Dec 19;17(1):481. doi: 10.1186/s12936-018-2629-2. (Open access available)

The effect of mobile phone text message reminders on health workers' adherence to case management guidelines for malaria and other diseases in Malawi: lessons from qualitative data from a cluster-randomized trial.

Kaunda-Khangamwa BN, Steinhardt LC, Rowe AK, Gumbo A, Moyo D, Nsona H, Troell P, Zurovac D, Mathanga D.
Malawi, South Africa, USA, Kenya, UK

BACKGROUND:
Mobile health (mHealth), which uses technology such as mobile phones to improve patient health and health care delivery, is increasingly being tested as an intervention to promote health worker (HW) performance. This study assessed the effect of short messaging services (SMS) reminders in a study setting. Following a trial of text-message reminders to HWs to improve case management of malaria and other childhood diseases in southern Malawi that showed little effect, qualitative data was collected to explore the reasons why the intervention was ineffective and describe lessons learned.

METHODS:
Qualitative data collection was undertaken to lend insight into quantitative results from a trial in which 105 health facilities were **randomized to three arms: (1) twice-daily text-message reminders to HWs, including clinicians and drug dispensers, on case management of malaria; (2) twice-daily text-message reminders to HWs on case management of malaria, pneumonia and diarrhoea; and, (3) a control arm**. In-depth interviews were conducted with 50 HWs in the intervention arms across seven districts. HWs were asked about acceptability and feasibility of the text-messaging intervention and its perceived impact on recommended case management. The interviews were recorded, transcribed and translated into English for a thematic and framework analysis. Nvivo 11 software was used for data management and analysis.

RESULTS:
A total of 50 HWs were interviewed at 22 facilities. HWs expressed high acceptance of text-message reminders and appreciated messages as job aids and practical reference material for their day-to-day work. **However, HWs said that health systems barriers, including very high outpatient workload, commodity stock-outs, and lack of supportive supervision and financial incentives demotivated them, limited their ability to act on messages and therefore adherence to case management guidelines.** Drug dispensers were more likely than clinicians to report usage of text-message reminders. Despite these challenges, nearly all HWs expressed a desire for a longer duration of the SMS intervention.

CONCLUSIONS:
Text-message reminders to HWs can provide a platform to improve understanding of treatment guidelines and case management decision-making skills, but might not improve actual adherence to guidelines. More interaction, for example through targeted supervision or two-way technology communication, might be an essential intervention component to help address structural barriers and facilitate improved clinical practice.

BMJ Glob Health. 2019 Mar 8;4(2):e001153. doi: 10.1136/bmjgh-2018-001153. eCollection 2019. (Open access available)

How and why front-line health workers (did not) use a multifaceted mHealth intervention to support maternal and neonatal healthcare decision-making in Ghana.

Amoakoh HB, Klipstein-Grobusch K, Ansah EK, Grobbee DE, Yveoo L, Agyepong I.

INTRODUCTION:
Despite increasing use of mHealth interventions, there remains limited documentation of 'how and why' they are used and therefore the explanatory mechanisms behind observed effects on beneficiary health outcomes. We explored 'how and why' an mHealth intervention to support clinical decision-making by front-line providers of maternal and neonatal healthcare services in a low-resource setting was used. The intervention consisted of phone calls (voice calls), text messaging (short messaging service (SMS)), internet access (data) and access to emergency obstetric and neonatalprotocols via an Unstructured Supplementary Service Data (USSD). It was delivered through individual-use and shared facility mobile phones with unique Subscriber Identification Module (SIM) cards networked in a Closed User Group.

METHODS:
A single case study with multiple embedded subunits of analysis within the context of a cluster randomised controlled trial of the impact of the intervention on neonatal health outcomes in the Eastern Region of Ghana was performed. We quantitatively analysed SIM card activity data for patterns of voice calls, SMS, data and USSD. We conducted key informant interviews and focus group discussions with intervention users and manually analysed the data for themes.

RESULTS:
Overall, the phones were predominantly used for voice calls (64%), followed by data (28%), SMS (5%) and USSD (2%), respectively. **Over time, use of all intervention components declined.** Qualitative analysis showed that individual health worker factors (demographics, personal and work-related needs, perceived timeliness of intervention, tacit knowledge), organisational factors (resource availability, information flow, availability, phone ownership), technological factors (attrition of phones, network quality) and client perception of health worker intervention usage explain the pattern of intervention use observed.

CONCLUSION:
How and why the mHealth intervention was used (or not) went beyond the technology itself and was influenced by individual and context-specific factors. These must be taken into account in designing similar interventions to optimise effectiveness.

Mhealth. 2019 Feb 25;5:7. doi: 10.21037/mhealth.2019.02.01. eCollection 2019. (Open access available)

Implementing the mobile continuing medical education (mCME) project in Vietnam: making it work and sharing lessons learned.

Bonawitz R, Bird L, Le NB, Nguyen VH, Halim N, Williams AL, Sabin L, Gill CJ.

BACKGROUND:
Mobile technology is a novel approach for delivering continuing medical education (CME), with numerous advantages including lower costs and the ability to reach larger numbers than traditional in-person CME workshops.

METHODS:
From May 2015 to May 2017, we conducted two randomized controlled trials in a phased approach to evaluate the effectiveness of a mobile CME (mCME) approach for two cadres of health professionals in Vietnam. **The first randomized controlled trial (RCT) tested the use of an SMS-based educational intervention among Community-Based Physician's Assistants; while feasible and acceptable, this intervention failed to improve medical knowledge among participants.** Given the failure of the first RCT, and drawing on qualitative work conducted with participants at the conclusion of the trial, various modifications were employed in the second RCT conducted among HIV specialist physicians in Vietnam. Version 2.0 of the mCME intervention did lead to significant improvement in medical knowledge among intervention participants. Here, we discuss in detail the development of an mCME platform and the experiential "lessons learned" during two phases of implementation.

RESULTS:
Numerous lessons were learned during implementation, including the importance of: (I) mixed methods approaches; (II) an underlying theoretical framework for behavior change projects; (III) expertise in software programming; (IV) aligning educational content to a well-defined participant population; and (V) engaging and motivating adult learners. We also discuss the critical importance of projects with local ownership and investment that are relevant to local problems.

CONCLUSIONS:
mHealth approaches for continued healthcare training and education is increasingly relevant in many low-resource settings, the lessons learned here will be valuable to other organizations looking to scale-up similar mHealth-type educational programmes.

Glob Health Sci Pract. 2018 Dec 27;6(4):693-710. doi: 10.9745/GHSP-D-18-00275. Print 2018 Dec 27. (Open access available)

mLearning in the Democratic Republic of the Congo: A Mixed-Methods Feasibility and Pilot Cluster Randomized Trial Using the Safe Delivery App.

Bolan NE, Sthreshley L, Ngoy B, Ledy F, Ntayingi M, Makasy D, Mbuyi MC, Lowa G, Nemeth L, Newman S.

USA, Democratic Republic of the Congo

BACKGROUND:
Substandard delivery care has been widely documented as a major cause of maternal mortality in health facilities globally. Health worker learning via mobile devices is increasing rapidly; however, there is little evidence of mLearning effectiveness. This study sought to determine the feasibility, acceptability, and potential effect of the Safe Delivery App (SDA) on health workers' practices in basic emergency obstetric and newborn care (BEmONC) in the Democratic Republic of the Congo (DRC). The Theoretical Domains Framework was used to guide this research.

METHODS:
Eight BEmONC facilities in central DRC were randomized to either an mLearning intervention or to standard practice (control). Maternal and newborn health workers in intervention facilities (n=64) were trained on the use of smartphones and the French version of the SDA. The SDA is an evidence-based BEmONC training resource with visual guidance using animated videos and clinical management instructions developed by the Maternity Foundation and the Universities of Copenhagen and Southern Denmark. Knowledge on postpartum hemorrhage (PPH) and neonatal resuscitation (NR) and self-confidence in performing 12 BEmONC procedures were assessed at baseline and at 3 months post-intervention. Eighteen qualitative interviews were conducted with app users and key stakeholders to assess feasibility and acceptability of mLearning and the use of the SDA. Maternal mortality was compared in intervention and control facilities using a smartphone-based Open Data Kit (ODK) data application. One smartphone with SDA and ODK was entrusted to intervention facilities for the study period, whereas control facilities received smartphones with ODK only.

RESULTS:
The analysis included 62 heath workers. Knowledge scores on postpartum hemorrhage and neonatal resuscitation increased significantly from baseline among intervention participants compared with controls at 3 months post-intervention (mean difference for PPH knowledge, 17.4 out of 100; 95% confidence interval [CI]=10.7 to 24.0 and 19.4 for NR knowledge; 95% CI=11.4 to 27.4), as did self-confidence scores on 12 essential BEmONC procedures (mean difference, 4.2 out of 48; CI=0.7 to 7.7). Increases were unaffected by health worker cadre and previous smartphone use. Qualitative interviews supported the feasibility and acceptability of the SDA and mLearning, and the potential for it to impact maternal and neonatal mortality in the DRC.

CONCLUSION:
Use of the Safe Delivery App supported increased health worker knowledge and self-confidence in the management of obstetric and newborn emergencies after 3 months. SDA and mLearning were found to be feasible and acceptable to health workers and key stakeholders in the DRC.

JMIR Mhealth Uhealth. 2019 Apr 2;7(4):e12652. doi: 10.2196/12652. (Open access available)

Improving Linkage to and Retention in Care in Newly Diagnosed HIV-Positive Patients Using Smartphones in South Africa: Randomized Controlled Trial.

Venter WDF, Fischer A, Lalla-Edward ST, Coleman J, Lau Chan V, Shubber Z, Phatsoane M, Gorgens M, Stewart-Isherwood L, Carmona S, Fraser-Hurt N.

BACKGROUND:
South Africa provides free antiretroviral therapy for almost 5 million people living with HIV, but only 71% of the eligible people are on treatment, representing a shortfall in the care cascade, especially among men and youth. Many developing countries have expanded access to smartphones; success in health apps raises the possibility of improving this cascade.

OBJECTIVE:
SmartLink is a health app for Android smartphones providing HIV-related laboratory results, information, support, and appointment reminders to engage and link patients to care. This study aimed to evaluate the ability of SmartLink to improve linkage to care for HIV-positive smartphone owners.

METHODS:
This study was a multisite randomized controlled trial in Johannesburg. The intervention arm received the app (along with referral to a treatment site) and the control arm received the standard of care (referral alone). Linkage to care was confirmed by an HIV-related blood test reported on the National Health Laboratory Service database between 2 weeks and 8 months after initiation.

RESULTS:
A total of 345 participants were recruited into the study; 64.9% (224/345) of the participants were female and 44.1% (152/345) were aged less than 30 years. In addition, 46.7% (161/345) were employed full time, 95.9% (331/345) had at least secondary school education, and 35.9% (124/345) were from Zimbabwe. Linkage to care between 2 weeks and 8 months was 48.6% (88/181) in the intervention arm versus 45.1% (74/164) in the control (P=.52) and increased to 64.1% (116/181) and 61.0% (100/164) (P=.55), respectively, after the initial 8-month period. Moreover, youth aged 18 to 30-years showed a statistically significant 20% increase in linkage to care for the intervention group.

CONCLUSIONS:
Youth aged less than 30 years have been historically difficult to reach with traditional interventions, and the SmartLink app provides a proof of concept that this population reacts to mobile health interventions that engage patients in HIV care.

Comment
For all the purported potential of smart-phone technology and e-health or m-mealth and its effect on health care, in reality the effects are less than the hope and the hype. Many of the above studies this year showed modest or no effects on patient engagement with health

information, minimal improvements in health care worker knowledge, decline in use of a novel App overtime (perhaps as the novelty wears off), and almost no effect of single text messages on health worker behaviour or parental care seeking. Such technologies are not isolated interventions, rather they are interposed into complex systems in which health workers function, and patients and caregivers interact with the health system, and where health care e-technologies often compete with the other social media environment that the health worker or family are exposed to and interact with. While there are many strengths of e-technology in providing precise, sometimes personalised, targeted information directly to the user, there are also flaws in every device and intervention, and these all mix into the flaws and strengths of the traditional health care systems.

Neurological disease and neurodevelopmental conditions

BMC Neurol. 2019 Mar 6;19(1):35. doi: 10.1186/s12883-019-1256-z. (Open access available)

Doxycycline for the treatment of nodding syndrome (DONS); the study protocol of a phase II randomised controlled trial.

Idro R, Anguzu R, Ogwang R, Akun P, Abbo C, Mwaka AD, Opar B, Nakamya P, Taylor M, Elliott A, Vincent A, Newton C, Marsh K.

BACKGROUND:
Nodding syndrome is a poorly understood neurological disorder of unknown aetiology, affecting several thousand children in Africa. There has been a consistent epidemiological association with infection by the filarial parasite, Onchocerca volvulus and antibodies to leiomodin and DJ-1, cross-reacting with O.volvulus proteins, have been reported. We hypothesized that **nodding syndrome is a neuro-inflammatory disorder, induced by antibodies to O.volvulus or its symbiont, Wolbachia, cross-reacting with human neuron proteins and that doxycycline, which kills Onchocerca through effects on Wolbachia, may be used as treatment.**

METHODS:
This will be a two-arm, double-blind, placebo-controlled, randomised phase II trial of doxycycline 100 mg daily for six weeks in 230 participants. Participants will be patients' ages≥8 years with nodding syndrome. They will receive standard of care supportive treatment. All will be hospitalised for 1-2 weeks during which time baseline measurements including clinical assessments, EEG, cognitive and laboratory testing will be performed and antiepileptic drug doses rationalised. Participants will then be randomised to either oral doxycycline (Azudox®, Kampala Pharmaceutical Industries) 100 mg daily or placebo. Treatment will be initiated in hospital and continued at home. Participants will be visited at home at 2, 4 and 6 weeks for adherence monitoring. Study outcomes will be assessed at 6, 12, 18 and 24-month visits. Analysis will be by intention to treat. The primary efficacy outcome measure will be the proportion of patients testing positive and the levels or titires of antibodies to host neuron proteins (HNPs) and/or leiomodin at 24 months. Secondary outcome measures will include effect of the intervention on seizure control, inflammatory markers, cognitive function, disease severity and quality of life.

DISCUSSION:
This trial postulates that targeting O.volvulus through drugs which kill Wolbachia can modify the pathogenic processes in nodding syndrome and improve outcomes. Findings from this study are expected to substantially improve the understanding and treatment of nodding syndrome.

Comment
This is the only trial protocol included in the summary booklet this year, because it is novel and the hypotethsis and methodology is very clearly outlined, and once conducted the trial will markedly increase our understanding of the pathophysiology of a complex neurological syndrome and the link with the microbial world.

Pediatr Neurosci. 2018 Oct-Dec;13(4):443-447. doi: 10.4103/JPN.JPN_60_18.

A Randomized Control Trial of Botulinum Toxin A Administration under Ultrasound Guidance against Manual Palpation in Spastic Cerebral Palsy.

Kaushik PS, Gowda VK, Shivappa SK, Mannapur R, Jaysheel A.
India

BACKGROUND:
Botulinum toxin A is established as an effective treatment to reduce spasticity in cerebral palsy (CP). But very little data are available regarding the techniques of administration. Hence, this study was conducted to compare administration of botulinum toxin with and without ultrasound.

MATERIALS AND METHODS:
This is a randomized trial conducted for 2 years at a tertiary care hospital in children aged up to 6 years with CP. Children were assessed with range of ankle dorsiflexion, Modified Ashworth Scale (MAS), and Gross Motor Function Measure 66 (GMFM 66) before and after administration. They were followed up for 6 months.

RESULTS:
Of the 180 children screened, 30 who met the criteria were included. Those enrolled in the study were categorized into group I and group II, children who were given botulinum toxin with ultrasound (n = 14) and without ultrasound (n = 16), respectively. Results showed a significant increase in ankle dorsiflexion in both groups ($P \leq 0.005$) but no significant difference was reported between the groups ($P = 0.4$). A statistically significant increase in GMFM scores ($P \leq 0.005$) during sequential assessment was observed in both groups, but no significant difference was observed in the GMFM scores between the groups ($P = 0.45$). Majority of children improved by a scale of 2 (MAS) from baseline in groups after 12 weeks, 50% in group I and 57.9% in group II.

CONCLUSION:

No significant difference was observed in the outcome with regard to technique of administration of botulinum toxin with ultrasound and without ultrasound into gastrocnemius muscle.

S Afr J Physiother. 2018 Aug 29;74(1):459. doi: 10.4102/sajp.v74i1.459. eCollection 2018. (Open access available)

The efficacy of kinesiology taping for improving gross motor function in children with cerebral palsy: A systematic review.

Unger M, Carstens JP, Fernandes N, Pretorius R, Pronk S, Robinson AC, Scheepers K.
South Africa.

Background:
Kinesiology taping is an increasingly popular technique used as an adjunct to physiotherapy intervention for children with cerebral palsy (CP), but as yet we do not have a review of the available evidence as to its efficacy.

Objectives:
To critically appraise and establish best available evidence for the efficacy of truncal application of kinesiology taping combined with physiotherapy, versus physiotherapy alone, on gross motor function (GMF) in children with CP.

Method:
Seven databases were searched using the terms CP, kinesio taping and/or kinesiology tape and/or taping, physiotherapy and/or physical therapy and GMF. Only randomised controlled trials (RCTs) were included and appraised using the PEDro scale. Revman© Review Manager was used to combine effects for GMF in sitting, standing and activities of daily living.

Results:
Five level IIB RCTs that scored 3-6/8 on the PEDro scale were included. Meta-analysis showed that taping was effective for improving GMF in sitting and standing as measured by the Gross Motor Function Measure (B) ($p < 0.001$) and (D) ($p < 0.001$), respectively.

Conclusion:
There is moderate evidence to support kinesiology taping applied to the trunk as an effective intervention when used as an adjunct to physiotherapy to improve GMF in children with CP, especially those with GMF Classification Scale levels I and II, and particularly for improving sitting control.
Clinical implications:
Kinesiology taping is a useful adjunct to physiotherapy intervention in higher functioning children with CP. Current evidence however is weak and further research into methods of truncal application is recommended.

Newborn care

Obstet Gynecol Sci. 2018 Nov;61(6):655-661. doi: 10.5468/ogs.2018.61.6.655. Epub 2018 Oct 29. (Open access available)

Safety of delayed umbilical cord clamping in preterm neonates of less than 34 weeks of gestation: a randomized controlled trial.

Rana A, Agarwal K, Ramji S, Gandhi G, Sahu L.
India

Objective:
There is concern regarding the safety of delayed cord clamping (DCC) in babies born at less than 34 weeks' gestation. Therefore, the primary objective of this study was to **compare the rates of hyperbilirubinemia and polycythemia during initial 7 days in infants born at less than 34 weeks' gestation and randomized to receive DCC by 120 seconds or early cord clamping (ECC) within less than 30 seconds**.

Methods:
One hundred pregnant women were randomly subjected to DCC or ECC at the time of birth in a tertiary referral hospital setting. Blood samples were obtained from each newborn at 48 hours and 7 days for hematocrit measurement. Serum bilirubin levels were estimated once the infant had clinically significant jaundice or at 72 hours. For the statistical analysis, the χ test, student's *t*-test, or Wilcoxon rank sum test was used.

Results:
The hematocrit was significantly higher in the DCC group than in the ECC group (P<0.001). None of the babies had polycythemia. Mean total serum bilirubin level was 6.6 mg/dL in the DCC group and 8.7 mg/dL in the ECC group (P<0.001). There was no increased risk of hyperbilirubinemia in the DCC group.

Conclusion:
DCC benefits preterm neonates with no significant adverse effects.

BMC Pediatr. 2018 Jul 18;18(1):234. doi: 10.1186/s12887-018-1214-8. (Open access available)

Early versus delayed cord clamping in small for gestational age infants and iron stores at 3 months of age - a randomized controlled trial.

Chopra A, Thakur A, Garg P, Kler N, Gujral K.
India.

BACKGROUND:
Delayed cord clamping is the standard of care in infants not requiring resuscitation; however effects of cord clamping strategies have not been evaluated systematically in small for

gestational age (SGA) infants. The primary objective was to compare effects of delayed cord clamping (DCC) and early cord clamping (ECC) on serum ferritin at 3 months in SGA infants born at ≥35 weeks. The secondary objectives were to compare hematological parameters, clinical outcomes in neonatal period and growth at 3 months of age.

METHODS:
All eligible infants with fetal growth restriction were randomized to two groups, DCC at 60 s or ECC group in which the cord was clamped immediately after birth.

RESULTS:
Total of 142 infants underwent randomization and subsequently 113 infants underwent definite inclusion. At 3 months, the median (IQR) serum ferritin levels were higher in DCC group, compared to ECC; 86 ng/ml (43.35-134.75) vs 50.5 ng/ml (29.5-83.5), p = 0.01. Fewer infants had iron deficiency in DCC group compared to ECC group; 9 (23.6%) vs 21 (47.7%), p = 0.03 [NNT being 4; 95% CI (2-25)]. The proportion of infants with polycythemia was significantly higher in DCC group; 23 (41.81) % vs 12 (20.6%), p = 0.01. There was no difference in proportion of infants with symptomatic polycythemia or those who underwent partial exchange transfusions. Clinical outcomes and mortality were similar.

CONCLUSIONS:
DCC improves iron stores in SGA infants ≥35 weeks at 3 months of age without increasing the risk of symptomatic polycythemia, need for partial exchange transfusions or morbidities associated with polycythemia.

Resuscitation. 2018 Sep;130:88-91. doi: 10.1016/j.resuscitation.2018.07.003. Epub 2018 Jul 5.

Umbilical cord milking in preterm neonates requiring resuscitation: A randomized controlled trial.

Ram Mohan G, Shashidhar A, Chandrakala BS, Nesargi S, Suman Rao PN.
India

OBJECTIVE:
To evaluate the effect of cord milking on short term morbidity and hematologic parameters at 6 weeks in preterm neonates requiring resuscitation.
METHODS:
This trial randomized preterm infants requiring resuscitation to milking group and no milking group. Multiple pregnancy, Rh negative mothers, hydrops, cord abnormalities were excluded. The primary outcome was hemoglobin and serum ferritin at 6 weeks of life. Secondary outcomes were common preterm morbidities and mortality.

RESULTS:
60 neonates were included in the study. Infants in the milking group had higher hemoglobin (10.07 g/dl vs 8.9 g/dl; p 0.003) and higher serum ferritin level (244.8 ng/ml vs 148.5 ng/ml; p 0.04) compared to no milking group.

CONCLUSIONS:
In preterm neonates requiring resuscitation, umbilical cord milking results in higher hemoglobin and ferritin at 6 weeks of life. It can be a used as a placental transfusion strategy in preterm neonates requiring resuscitation with no significant adverse effects.

J Perinatol. 2018 Sep;38(9):1190-1196. doi: 10.1038/s41372-018-0161-4. Epub 2018 Jul 5.

Umbilical cord milking for neonates who are depressed at birth: a randomized trial of feasibility.

Girish M, Jain V, Dhokane R, Gondhali SB, Vaidya A, Aghai ZH.
India, USA

OBJECTIVE:
To evaluate the feasibility and safety of umbilical cord milking (UCM) in neonates who are depressed at birth.

STUDY DESIGN:
This is a quasi-randomized, non-blinded, controlled trial on infants (≥35 weeks) who were depressed at birth. UCM (cord milked three times) was performed during the even months and the neonates born during the odd months were in the control group. Primary outcome was feasibility and safety.

RESULTS:
A total of 101 infants were enrolled (50 UCM group and 51 control group) between January 2015 and October 2016. UCM was performed in 95% of infants (59/62) who qualified to receive UCM. There were no significant differences in resuscitation delay, resuscitation efforts, and short-term outcomes between the two groups.

CONCLUSIONS:
UCM is feasible for term and late preterm infants who are depressed at birth. A larger clinical trial is needed to evaluate long-term benefits of UCM in neonates with HIE.

*** Int J Health Sci (Qassim). 2019 Jan-Feb;13(1):40-51. (Open access available)

Effect of chlorhexidine cord application on prevention of neonatal sepsis in developing countries: Systematic review and meta-analysis.

Gelano TF, Bacha YD, Abate D.

OBJECTIVE:
The aim of this review was to identify the pooled effect of chlorhexidine cord application on prevention of neonatal sepsis in developing countries.

METHODS:
We have conducted systemic review and meta-analysis. Articles were searched from electronic databases such as PubMed, EMBASE, CINHAL, Cochrane central register of controlled trials (CENTRAL), and other sources such as direct Google search, Google Scholar, and POPline. Only randomized controlled trial studies were considered for this review. The effect of chlorhexidine cord application on prevention of neonatal sepsis and mortality was assessed as compared to dry cord care.

RESULTS:
Five studies from developing countries were included in the review with a total of 129,293 participants. **Pooled result of meta-analysis showed that chlorhexidine cord application reduces neonatal sepsis by 32% as compared to dry cord care** (relative risk [RR] 0.68, 95% confidence interval [CI] 0.57-0.81, random effect model, I =93%). It also indicated that **chlorhexidine cord application reduces severe sepsis by 77% (RR 0.23, 95% CI 0.11-0.48, random effect model, I = 63%) and neonatal mortality reduction by 13 % as compared to dry cord care (RR 0.87, 95% CI 0.79-0.97, random effect model, I = 0%).**

CONCLUSIONS:
Chlorhexidine cord application significantly reduces neonatal sepsis and mortality in developing countries. Therefore, we stress the importance of including chlorhexidine cord application into the essential newborn care in the setting with high burden of neonatal mortality. The review protocol was registered at PROSPERO with registration number CRD 42018089204.

PLoS One. 2018 Sep 27;13(9):e0204902. doi: 10.1371/journal.pone.0204902. eCollection 2018. (Open access available)

Care-seeking practices for sick neonates: Findings from cross-sectional survey in 14 rural sub-districts of Bangladesh.

Chowdhury SK, Billah SM, Arifeen SE, Hoque DME.
Bangladesh.

OBJECTIVES:
Neonatal deaths account for 45% of all under-five deaths globally and 60% in Bangladesh. This study aimed to investigate the most common symptoms and complications in neonates, care-seeking practices of the mothers for their sick neonates, and factors associated with the care-seeking practices.

METHODS:
This cross-sectional study analysed data from an Endline Household Survey (as part of an evaluation of a paired cluster-randomised controlled trial study in 14 rural sub-districts in Bangladesh) of 2,931 women who gave birth recently. Descriptive analysis and logistic regressions were conducted to identify the care-seeking practices of mothers of sick neonates and the factors associated with the care-seeking from trained providers.

RESULTS:

Of the 2868 neonates, 886 (30.9%) were reported ill during first 28 days after birth. For those with reported symptoms, 748 (84.4%) of their mothers sought care. Of those who sought care, 65.2% sought care from untrained providers. Multiple logistic regression analysis showed significantly **higher odds of care-seeking from trained providers when neonates had 3 or more concurrent symptoms (OR: 1.82; 95% CI: 1.07-3.08); when mothers perceived their neonates' symptoms as severe (OR: 4.08; 95% CI: 2.92-5.70); when mothers received skilled care during pregnancy (OR: 1.95; 95% CI: 1.34-2.84); and when mothers had their delivery in a facility (OR: 3.50; 95% CI: 2.18-5.62).** Mothers who delivered their babies at a facility, 43.1% of them sought care for their sick neonates at the same type of public hospital and 34.9% from same type of private hospitals where their deliveries took place.

CONCLUSION:
Skilled care for mothers during pregnancy and delivery, and mothers' perceptions of the severity of symptoms are the key associated factors of care-seeking for sick neonates from trained providers. Interventions should be tailored to increase care from trained providers during pregnancy and delivery at facilities to improve care-seeking for neonates from trained providers and for the survival of neonates.

PLoS One. 2018 Nov 15;13(11):e0207206. doi: 10.1371/journal.pone.0207206. eCollection 2018. (Open access available)

Feasibility assessment of an ergonomic baby wrap for kangaroo mother care: A mixed methods study from Nepal.

Thapa K, Mohan D, Williams E, Rai C, Bista S, Mishra S, Hamal PK.
USA, Nepal.

BACKGROUND:
Kangaroo mother care, an evidence based practice and a national policy for management of low birth weight newborns in Nepal, is not widely practiced. This implementation research study aimed to explore the consumer preference and acceptability of the traditional and a new ergonomic wrap on the continuation of kangaroo mother care in the facility and community following discharge.

METHODS:
A mixed method feasibility study was done from May to October 2015. Ninety-six families of stable low birth weight newborns weighing 1800 to 2499 grams were counseled and taught to practice kangaroo mother care using both wraps. **They were randomized into two groups of 48 with one group trying out the traditional wrap for the first six hours and the new wrap for the next six, and vice versa.** Mothers were allowed to choose between the wraps for continuation of kangaroo mother care at the facility and post discharge. They were followed up telephonically weekly over 28 days postpartum to ascertain practice of kangaroo mother care. In-depth interviews with mothers (n = 12) and focus group discussions with health workers (n = 16) further evaluated the intervention. Descriptive statistics are presented for the quantitative part of the study.

RESULTS:
Mothers in the two groups chose the new wrap with no significant difference (81.3% vs 89.6%, p = 0.24). Of the 96 randomized mothers, 85% chose the new wrap. During the hospital stay, six mothers dropped out and remaining 90 mothers who were discharged with the intention of continuing Kangaroo Mother Care, 78 and 12 mothers did so with the new and traditional wrap respectively. New wrap users (429.1 hours, 95% confidence interval [CI]: 351.7-470.3) performed skin-to-skin contact for an extra 77.4 hours overall than traditional wrap (351.7 hours, 95%CI: 259.3-444) users from first day to 28 day postpartum. Health workers and mothers reported positive experience with the new wrap as it was easy to wear without assistance, secure and flexible to move around in kangaroo mother care position.
CONCLUSIONS:
Involvement of mothers and families with provision of ergonomic wraps showed improvement in kangaroo mother care practice during hospital stay and at home.

Neonatal intensive care – general

J Perinatol. 2019 Jan;39(1):95-101. doi: 10.1038/s41372-018-0249-x. Epub 2018 Oct 22. (Open access available)

Does ultrasound guidance for peripherally inserted central catheter (PICC) insertion reduce the incidence of tip malposition? - a randomized trial.

Oleti T, Jeeva Sankar M, Thukral A, Sreenivas V, Gupta AK, Agarwal R, Deorari AK, Paul VK. India

OBJECTIVE:
The aim of the study was to evaluate the incidence of peripheral inserted central catheter (PICC) tip malposition when the catheter is inserted under real-time ultrasound (RTUS) guidance when compared with conventional landmark (CL) technique in neonates. Additional objectives were to evaluate the PICC longevity and central line associated blood stream infections (CLABSI).

STUDY DESIGN:
In this randomised controlled trial, neonates were randomised to 'RTUS' (n = 40) or 'CL' (n = 40) groups. PICC tip was placed under ultrasound guidance in lower third of superior vena cava in the RTUS group. In 'CL' group, PICC was inserted as calculated by anatomical landmarks.

RESULTS:
The birth weight (1286 (926, 1662) vs. 1061 (889, 1636) g) and gestation (31.12 (3.1) vs. 31.4 (3.6) wks) were comparable among the groups. **RTUS guidance during PICC insertion reduced incidence of tip malposition by 52% (67.5 vs. 32.5%; RR: 0.48; 95% CI: 0.29-0.79).** The longevity of PICC and episodes of CLABSI were however similar in the two groups.

CONCLUSIONS:

Real-time ultrasound guidance during PICC placement reduces the incidence of tip malposition.

Acta Paediatr. 2018 Dec;107(12):2071-2078. doi: 10.1111/apa.14567. Epub 2018 Oct 2. (Open access available)

Randomised controlled trial showed that neonates received better pain relief from a higher dose of sucrose during venepuncture.

Kristoffersen L, Malahleha M, Duze Z, Tegnander E, Kapongo N, Støen R, Follestad T, Eik-Nes SH, Bergseng H.
Norway, South Africa

AIM:
We compared the effect of two different doses of sucrose on neonatal pain scores during venepuncture.

METHODS:
This randomised crossover study focused on neonates born weighing more than 1000 g from December 2014 to June 2016, who received neonatal intensive care at two hospitals: one in Empangeni, South Africa, and one in Trondheim, Norway. During two consecutive venepuncture procedures, 27 neonates from South Africa and 26 neonates from Norway were randomised to receive 0.2 mL or 0.5 mL sucrose. Half was administered two minutes before venepuncture and the rest immediately before the procedure. South Africa used 25% sucrose and Norway 24%. Pain scores were measured twice using the Premature Infant Pain Profile-Revised: during skin puncture and after the needle was removed.

RESULTS:
The mean pain scores during skin puncture were significantly lower with 0.5 mL sucrose than with 0.2 mL (5.3 versus 6.8, p=0.008), but the mean pain scores after the needle was removed were similar with both doses (4.7 versus 5.4, p=0.29). We found no significant association between weight and pain scores.

CONCLUSION:
We showed that neonates received better pain relief from 0.5 mL than 0.2 mL sucrose during venepuncture but not after the needle was removed.

Nutrition. 2018 Dec 11. pii: S0899-9007(18)30965-1. doi: 10.1016/j.nut.2018.12.006. [Epub ahead of print]

Two parenteral amino acid solutions and plasma levels of amino acids in the neonate: A randomized trial.

Anaya-Flórez MS, Barbosa-Cortés L, Villasis-Keever MA, Aguilar-Monroy S, Montalvo-Velarde I, López-Alarcón M, Lledias-Corona M, Huerta-Tecanhuey A, Maldonado-Hernández J, Madrigal-Muñiz O, González-Cabello H.

OBJECTIVE:
In neonates on total parenteral nutrition (TPN), amino acids may be a risk factor for developing total parenteral nutrition-associated cholestasis (TPNAC). We aimed, first, to compare methionine, cysteine, and taurine plasma levels between neonates on TPN who were receiving an intravenous amino acid solution based on a breast milk aminogram and those on an intravenous solution of pediatric amino acids based on an umbilical cord aminogram, and second, to determine the frequency of TPNAC.

METHODS:
A double-blind randomized controlled trial was conducted. Ninety-four neonates with a birthweight of 1000g or more and a gestational age of 30 wk or older were admitted and enrolled. Blood samples were obtained at 0, 7, and 14 d of TPN, and plasma amino acid concentrations were determined by ultra-high-resolution liquid chromatography. Continuous variables were compared using the Wilcoxon rank-sum test or Student's t test; categorical variables were compared using the Fisher exact test.

RESULTS:
Thirty-five neonates completed the study (Primene, n = 14; TrophAmine, n = 21). On day 14, methionine plasma concentrations were significantly lower in the Primene group than in the TrophAmine group (27 µmol/L versus 32.9 µmol/L, P = 0.044); the taurine concentration was significantly higher in the same group (72.4 µmol/L versus 45.3 µmol/L, P < 0.0001). There were no differences in TPNAC incidence.

CONCLUSIONS:
Administering an intravenous solution of pediatric amino acids based on the umbilical cord aminogram yielded a higher taurine and lower methionine plasma concentration than did administering a similar solution based on the breast milk aminogram.

Arch Dis Child Fetal Neonatal Ed. 2018 Oct 15. pii: fetalneonatal-2018-315345. doi: 10.1136/archdischild-2018-315345. (Open access available)

Continuous infusion versus intermittent bolus doses of fentanyl for analgesia and sedation in neonates: an open-label randomised controlled trial.

Abiramalatha T, Mathew SK, Mathew BS, Shabeer MP, Arulappan G, Kumar M, Jayaseelan V, Kuruvilla KA.
India

OBJECTIVE:
Adequate data on fentanyl pharmacokinetics in neonates are lacking. The study was performed to compare serum concentrations and clinical outcome between continuous

infusion (CI) and intermittent bolus (IB) doses of fentanyl for analgesia and sedation in neonates.

METHODS:
In this open-label randomised controlled trial, neonates requiring 24-48 hours of mechanical ventilation and fentanyl administration were recruited. In CI regimen, 1 mcg/kg loading dose was followed by 1 mcg/kg/hour infusion. In IB regimen, 1mcg/kg/dose was administered every 4 hours.Maximum six blood samples were collected in 48 hours from each baby at prespecified time points for estimating serum fentanyl concentration. Secondary outcomes were pain scores (Neonatal Infant Pain Scale and Neonatal Pain, Agitation and Sedation Scale for acute and ongoing pain, respectively) and incidence of adverse effects of fentanyl.

RESULTS:
100 neonates were recruited, 53 in CI and 47 in IB group. In CI regimen, median (IQR) serum fentanyl concentration was 0.42 (0.35, 0.46) to 0.61 (0.47, 0.89) ng/mL throughout the infusion period. In IB regimen, median (IQR) peak concentration ranged from 2.21 (1.82, 3.55) to 3.61 (2.91, 4.51) ng/mL and trough concentration 0.41 (0.33, 0.48) to 0.97 (0.56, 1.25) ng/mL for various doses.Median (IQR) peak concentration (C_{max}, 3.06 (1.09, 4.50) vs 0.78 (0.49, 1.73) ng/mL; p<0.001) was significantly higher and area under concentration-time curve (AUC_{0-24}, 19.6 (10.4, 33.5) vs 13.2 (10.8, 22.6) µg·hour/L; p=0.12) was higher (though not statistically significant) in IB than CI regimen. Pain scores and adverse effects were comparable between the two regimens.

CONCLUSION:
CI regimen of fentanyl produces steady serum concentrations, whereas IB regimen produces wide fluctuations in serum concentration with high-peak concentrations. A serum fentanyl concentration of 0.4-0.6 ng/mL produces adequate analgesia and sedation in neonates.

Low birth weight and prematurity

J Matern Fetal Neonatal Med. 2018 Nov 28:1-171. doi: 10.1080/14767058.2018.1554046.
(Open access available)

A randomized controlled trial comparing the effect of fortification of human milk with an infant formula powder versus unfortified human milk on the growth of preterm very low birth weight infants.

Gupta V, Rebekah G, Sudhakar Y, Santhanam S, Kumar M, Thomas N.
India.

OBJECTIVE:
To optimize growth in very low birth weight (VLBW) infants, human milk fortification is standard of care in neonatal units of high income countries. However, commercial fortifiers may not be available or it may be too expensive in resource limited settings. **As an alternative to using human milk fortifiers, we studied the effects of milk fortification**

with an infant formula on growth and biochemical parameters of very low birth weight (VLBW) infants Methods: We undertook a prospective, randomized controlled trial in the neonatal unit of a tertiary care hospital in south India. Preterm infants weighing < 1500 grams and < 34 weeks of gestation were randomized after stratification according to birth weight into two groups (< 1250 g and 1250 to < 1500 g). **One group received fortified human milk while the other received exclusive human milk.** Fortification was done with a commercially available infant milk powder added to expressed breast milk (when the infant reached 150 ml/kg/day of feeds) and continued till the infant reached 1800 g. Primary outcome was rate of weight gain/kg/day. Secondary outcome measures were linear growth, head circumference increase, biochemical parameters to assess the adequacy or excess of protein supplementation and comorbidities like feed intolerance, sepsis and necrotizing enterocolitis (NEC).

RESULTS:
Total of 163 babies were randomized during the study period, of whom 148 babies (73 in the standard arm and 75 in the fortification arm) completed the trial. Baseline demographic data among the two groups were comparable. **Weight gain/kg/day (mean difference (MD) 1.98 g/kg/day; 95% CI 1.03 to 2.92; p < 0.001) and linear growth (MD 0.09cm/week; 95% CI 0.02 to 0.2; p = 0.02) was significantly higher in the fortification arm as compared to the control arm.** The head growth (head circumference gain in cm/week) was higher and length of hospital stay lesser in the fortification arm, though not statistically significant. Biochemical parameters, rates of sepsis, feed intolerance and necrotizing enterocolitis (NEC) were not different between the two groups.

CONCLUSION:
Fortification with Infant milk powder achieves better growth parameters than unfortified human milk and can be a useful alternative for feeding preterm VLBW infants in low resource settings.

Pregnancy Childbirth. 2019 Jan 8;19(1):12. doi: 10.1186/s12884-018-2128-z. (Open access available)

The assessment of gestational age: a comparison of different methods from a malaria pregnancy cohort in sub-Saharan Africa.

Unger H, Thriemer K, Ley B, Tinto H, Traoré M, Valea I, Tagbor H, Antwi G, Gbekor P, Nambozi M, Kabuya JB, Mulenga M, Mwapasa V, Chapotera G, Madanitsa M, Rulisa S, de Crop M, Claeys Y, Ravinetto R, D'Alessandro U.
UK, Australia, Belgium, Burkina Faso, Ghana, Zambia, Malawi, Rwanda

BACKGROUND:
Determining gestational age in resource-poor settings is challenging because of limited availability of ultrasound technology and late first presentation to antenatal clinic. Last menstrual period (LMP), **symphysio-pubis fundal height (SFH)** and Ballard Score (BS) at delivery are therefore often used. **We assessed the accuracy of LMP, SFH, and BS to estimate gestational age at delivery and preterm birth compared to ultrasound (US)**

using a large dataset derived from a randomized controlled trial in pregnant malaria patients in four African countries.

METHODS:
Mean and median gestational age for US, LMP, SFH and BS were calculated for the entire study population and stratified by country. Correlation coefficients were calculated using Pearson's rho, and Bland Altman plots were used to calculate mean differences in findings with 95% limit of agreements. Sensitivity, specificity, positive predictive value and negative predictive value were calculated considering US as reference method to identify term and preterm babies.

RESULTS:
A total of 1630 women with P. falciparum infection and a gestational age > 24 weeks determined by ultrasound at enrolment were included in the analysis. The mean gestational age at delivery using US was 38.7 weeks (95%CI: 38.6-38.8), by LMP, 38.4 weeks (95%CI: 38.0-38.9), by SFH, 38.3 weeks (95%CI: 38.2-38.5), and by BS 38.0 weeks (95%CI: 37.9-38.1) ($p < 0.001$). Correlation between US and any of the other three methods was poor to moderate. **Sensitivity and specificity to determine prematurity were 0.63 (95%CI 0.50-0.75) and 0.72 (95%CI, 0.66-0.76) for LMP, 0.80 (95%CI 0.74-0.85) and 0.74 (95%CI 0.72-0.76) for SFH and 0.42 (95%CI 0.35-0.49) and 0.77 (95%CI 0.74-0.79) for BS.**

CONCLUSIONS:
In settings with limited access to ultrasound, and in women who had been treated with P. falciparum malaria, **SFH may be the most useful antenatal tool to date a pregnancy when women present first in second and third trimester**. The Ballard postnatal maturation assessment has a limited role and lacks precision. Improving ultrasound facilities and skills, and early attendance, together with the development of new technologies such as automated image analysis and new postnatal methods to assess gestational age, are essential for the study and management of preterm birth in low-income settings.

Indian Pediatr. 2018 Jul 15;55(7):568-572.

Comparison of Three Nursing Positions for Reducing Gastric Residuals in Preterm Neonates: A Randomized Crossover Trial.

Kaur V, Kaur R, Saini SS.
India

OBJECTIVE:
To compare left lateral, right lateral, and prone nursing positions of neonate for reducing pre-feed gastric residuals among ≤34 weeks neonates.

DESIGN:
Randomized crossover trial.

SETTING:

Level-III NICU.

PARTICIPANTS:
Neonates ≤34 weeks, receiving 50-150 mL/kg/day feeds through oro-gastric route.

INTERVENTION:
Neonates were randomized to left lateral, right lateral and prone positions. Intervention position was given for eight hours (4 feeds, 9AM to 5PM) followed by a wash-off period of 16 hours. After 24 hours, each neonate crossed over to next position as per randomization card to complete three positions in three consecutive days. Gastric residuals were collected just before next feed.

OUTCOME MEASURES:
Pre-feed gastric residuals.

RESULTS:
Sixty three neonates were randomized. Fewer neonates in right lateral position had gastric residuals compared to left lateral position [OR 0.09 (95% CI 0.04, 0.21), P<0.001]. Neonates in right lateral and prone positions had comparable gastric residuals [OR 0.90 (95% CI 0.36, 2.22), P=0.82]. **Gastric residuals, as a proportion of last feed, were highest in left lateral [6% (2, 10), maximum 28%] position.** Significantly higher proportion of neonates in right lateral position had episodes of regurgitation compared to other positions. Oxygen saturation, heart rate, time to full feeds and duration of hospital stay were comparable in the three groups.

CONCLUSIONS:
Left lateral position was associated with higher but clinically non-significant pre-feed gastric residuals as compared to right lateral position. Right lateral position was associated with significantly increased regurgitation episodes.

Adv Neonatal Care. 2018 Aug;18(4):E13-E19. doi: 10.1097/ANC.0000000000000532.

Gastric Residual Volumes Versus Abdominal Girth Measurement in Assessment of Feed Tolerance in Preterm Neonates: A Randomized Controlled Trial.

Thomas S, Nesargi S, Roshan P, Raju R, Mathew S, P S, Rao S.
India

BACKGROUND:
Preterm neonates often have feed intolerance that needs to be differentiated from necrotizing enterocolitis. Gastric residual volumes (GRV) are used to assess feed tolerance but with little scientific basis.

PURPOSE:

To compare prefeed aspiration for GRV and prefeed measurement of abdominal girth (AG) in the time taken to reach full feeds in preterm infants.

METHODS:
This was a randomized controlled trial. Infants with a gestational age of 27 to 37 weeks and birth weight of 750 to 2000 g, who required gavage feeds for at least 48 hours, were included. Infants were randomized into 2 groups: infants in the AG group had only prefeed AG measured. Those in the GRV group had prefeed gastric aspiration obtained for the assessment of GRV. The primary outcome was time to reach full enteral feeds at 150 mL/kg/d, tolerated for at least 24 hours. Secondary outcomes were duration of hospital stay, need for parenteral nutrition, episodes of feed intolerance, number of feeds withheld, and sepsis.

RESULTS:
Infants in the AG group reached full feeds earlier than infants in the GRV group (6 vs 9.5 days; P = .04). No significant differences were found between the 2 groups with regard to secondary outcomes.

IMPLICATIONS FOR PRACTICE:
Our research suggests that measurement of AG without assessment of GRV enables preterm neonates to reach full feeds faster than checking for GRV.

IMPLICATIONS FOR RESEARCH:
Abdominal girth measurement as a marker for feed tolerance needs to be studied in infants less than 750 g and less than 26 weeks of gestation.

J Hum Nutr Diet. 2018 Oct;31(5):612-624. doi: 10.1111/jhn.12585. Epub 2018 Aug 2.

Effect of oropharyngeal colostrum therapy in the prevention of necrotising enterocolitis among very low birthweight neonates: A meta-analysis of randomised controlled trials.

Garg BD, Balasubramanian H, Kabra NS, Bansal A.
India

BACKGROUND:
Necrotising enterocolitis (NEC) is one of the most common life-threatening emergencies of the gastrointestinal tract in preterm neonates. The present study aimed to determine the efficacy of oropharyngeal colostrum with respect to reducing NEC in preterm neonates.
METHODS:
A literature search was conducted for various randomised control trials by searching the Cochrane Central Register of Controlled Trials, PubMed, EMBASE and ongoing clinical trials. Randomised or quasi-randomised trials comparing oropharyngeal colostrum versus placebo in neonates (birthweight ≤ 1500 g or gestational age ≤ 32 weeks) were included in the review. The methodological quality of each trial was independently reviewed by the authors. For categorical and continuous variables, typical estimates for relative risk and typical estimates

for weighted mean difference were calculated, respectively. A random effect model was assumed for meta-analysis.

RESULTS:
In total, four eligible trials were included in the review. Oropharyngeal colostrum therapy was not associated with a statistically significant reduction in the incidence of NEC stage ≥2 [typical relative risk (RR) = 0.64; 95% confidence interval (CI) = 0.27-1.49], mortality from any cause (typical RR = 0.86; 95% CI = 0.15-4.80) and time to reach full feed [typical weighted mean difference (WMD) = -3.26; 95% CI = -8.87 to 2.35]. Duration of hospital stay was significantly less in the control group (typical WMD = 9.77; 95% CI = 3.96-15.59).

CONCLUSIONS:
The current evidence is insufficient for recommending oropharyngeal colostrum as a routine clinical practice in the prevention of NEC. We emphasise the need for large randomised controlled trials with an adequate sample size and validated clinical outcomes in preterm neonates.

J Trop Pediatr. 2019 May 10. pii: fmz028. doi: 10.1093/tropej/fmz028. [Epub ahead of print] (Open access available)

Exclusive Breast Milk vs. Hybrid Milk Feeding for Preterm Babies- A Randomized Controlled Trial Comparing Time to Full Feeds.

Nandakumar A, Pournami F, Prabhakar J, Nair PMC, Jain N.

Abstract
When breastmilk is insufficient to meet planned feed volumes, neonatologists need to continue parenteral nutrition (PN) or use formula. This trial conducted at a tertiary care unit in South India between August 2014 and April 2016 compared time to full feeds in preterms fed 'mother's milk alone(MM)' vs. 'hybrid feed-mother's milk supplemented with formula(HF)'. We also compared time to regain birth weights, duration of PN, feed intolerance, Necrotizing Enterocolitis stage 2 or more, all-cause mortality, Extrauterine growth restriction, Healthcare associated infections, exclusive breast milk feeding rates at discharge, Retinopathy of prematurity requiring laser therapy, abnormal neurosonogram and oxygen dependency at 28 days. Neonates between 27 and 32 weeks were randomized into MM/HF when breast milk was insufficient. HF received formula to reach targeted feed volumes. MM received more PN to meet fluid requirements. 54 babies were analyzed in MM and 58 in HF. Time to full feeds were similar-MM (14.1 ± 4 days); HF (13.5 ± 4 days), p = 0.45**. Exclusive breast milk feeding rates at discharge were higher in MM when compared to HF (74% vs. 51%).** Other secondary outcomes were similar between groups. When mother's milk is unavailable in sufficient quantities, preterm babies may receive hybrid feeds.

Neonatology. 2019;115(3):256-262. doi: 10.1159/000496015. Epub 2019 Jan 30. (Open access available)

Early Total Enteral Feeding versus Conventional Enteral Feeding in Stable Very-Low-Birth-Weight Infants: A Randomised Controlled Trial.

Nangia S, Vadivel V, Thukral A, Saili A.
India

OBJECTIVE:
To evaluate the effect of early total enteral feeding (ETEF) when compared with conventional enteral feeding (CEF) in stable very-low-birth-weight (VLBW; 1,000-1,499 g) infants on the postnatal age (in days) at attaining full enteral feeds.

METHODS:
In this unblinded randomised controlled trial, 180 infants were allocated to an ETEF (n = 91) or a CEF group (n = 89). Feeds were initiated as total enteral feeds in the ETEF group and as minimal enteral nutrition (20 mL/kg) in the CEF group. The rest of the day's requirement in the CEF group was provided as parenteral fluids. The primary outcome was postnatal age at attaining full enteral feeds. The secondary outcomes included episodes of feed intolerance, incidence of sepsis and necrotising enterocolitis (NEC), and duration of hospital stay.

RESULTS:
The baseline variables including birth weight and gestational age were similar in the two groups. The infants of the ETEF group attained full enteral feeds earlier than those of the CEF group (6.5 ± 1.5 vs. 10.1 ± 4.1 days postnatal age; mean difference -3.6 [-4.5 to -2.7]; p < 0.001). Total episodes of feed intolerance and clinical sepsis were fewer, with a shorter duration of hospital stay, in the ETEF group (15.5 vs. 19.6 days) (p = 0.01). The incidence of NEC was similar in the two groups.

CONCLUSION:
ETEF in stable VLBW infants results in earlier attainment of full feeds and decreases the duration of hospital stay without any increased risk of feed intolerance or NEC.

Indian Pediatr. 2019 Apr 15;56(4):294-298.

Early Aggressive Enteral Feeding in Neonates Weighing 750-1250 Grams: A Randomized Controlled Trial.

Modi M, Ramji S, Jain A, Kumar P, Gupta N.
India

BACKGROUND:
In preterm neonates, enteral feeding is advanced slowly, considering the risk of necrotizing enterocolitis. Prolonged intravenous alimentation in these neonates, however, may increase the risk of sepsis-related morbidity and mortality, particularly in low resource settings.

OBJECTIVES:

Objective of this was study to evaluate impact of aggressive enteral feeding on mortality and morbidities among preterm neonates.

DESIGN:
Randomized controlled trial.

PARTICIPANTS:
Neonates with birthweight 750-1250 g.

INTERVENTIONS:
131 preterm neonates with birth weight 750-1250 g, admitted to neonatal intensive care unit between April 2012 and June 2014, were randomized to aggressive feeding or conservative feeding regimen.

OUTCOMES:
The primary outcome of the study was all-cause mortality during hospital stay. The secondary outcomes included proportion of sepsis (blood culture proven), necrotizing enterocolitis, feed intolerance, survival without major morbidity at discharge, time to reach full enteral feed (180 mL/kg/d), duration of hospitalization, and average daily weight gain (g/kg).

RESULTS:
All-cause mortality was 33.3% in aggressive regimen and 43.1% in conservative regimen, [RR (95%) CI 0.77 (0.49, 1.20)]. Neonates with aggressive feeding regimen reached full enteral feed earlier; median (IQR) 7 (6, 8) days compared to conservative regimen, 10 (9, 14) days; P <0.001. There was no difference in culture positive sepsis rate, survival without major morbidities, feed intolerance, necrotizing enterocolitis, duration of hospitalization and average daily weight gain.

CONCLUSIONS:
In neonates with birth weight 750-1250 g, early aggressive feeding regimen is feasible but not associated with significant reduction in all-cause mortality, culture positive sepsis or survival without major morbidities during hospital stay. **Neonates with aggressive regimen have fewer days on IV fluids and reach full feed earlier.**

Kathmandu Univ Med J (KUMJ). 2017 Oct.-Dec.;15(60):319-323.

Placebo Controlled Introduction of Prophylactic Supplementation of Probiotics to Decrease the Incidence of Necrotizing Enterocolitis at Dhulikhel Hospital in Nepal.

Dongol Singh S S , Klobassa DS , Resch B , Urlesberger B , Shrestha RP .
Nepal, Austria

Abstract

Background Although recent reports suggest that the use of probiotics may enhance intestinal functions in premature infants, the mechanisms are unclear, and open questions remain regarding the safety and its efficacy.
Objective The objective of this study is to **evaluate the efficacy of probiotics on prevention of necrotizing enterocolitis in preterm infants in Nepal**. Method We conducted a randomized, double blind, placebo controlled study of 72 hospitalized preterm infants. **They were randomly allocated to receive probiotics (lactobacillus rhamnosus 35) at a dose of 0.8 mg in infants >1500 gms and 0.4 mg in infants <1500 gms in 2 ml of expressed breast milk two times daily or the same amount of expressed breast milk as placebo (without probiotics).**
Result Seventy-two patients were studied. The probiotics group (n=37) and placebo group (n=35) showed similar clinical characteristics. **The incidence of necrotizing enterocolitis was found less frequently in the probiotic group (6/37, 16.2%) compared to the control group (10/35, 28.6%), this difference was not significant (p=0.16).** This is 12.35% reduction in the incidence of necrotizing enterocolitis. Among the risk factors for necrotizing enterocolitis, pregnancy risk factors and perinatal risk factors were not significant. However neonatal risk factors were more frequent in the probiotic group (59.3%, n=32) than in the placebo group (40.7%, n=22), the difference was significant (p=0.02).
Conclusion In the western world probiotics have been shown to be preventive in regard to necrotizing enterocolitis incidence. The present randomized trial showed a trend towards necrotizing enterocolitis minimal reduction in Nepal too. Further studies in a larger cohort are warranted to prove this effect for preterm infants.

Indian Pediatr. 2018 Aug 15;55(8):675-678. (Open access available)

Prefeeding Oromotor Stimulation Program for Improving Oromotor Function in Preterm Infants - A Randomized Controlled Trial.

Arora K, Goel S, Manerkar S, Konde N, Panchal H, Hegde D, Mondkar J.
India, Australia.

OBJECTIVE:
To determine effect of Premature Infant Oral Motor Intervention program on oro-motor function and time to full independent wati spoon feeds in preterm infants.

METHODS:
30 preterm infants between 28-32 weeks of gestation on full gavage feeds of 150 mL/kg/day were randomized to receive either pre-feed oro-motor stimulation using Premature Infant Oral Motor Intervention (structured stimulation) or sham intervention (unstructured stimulation).

RESULTS:
Improvement in mean (SD) Neonatal Oro-Motor Assessment Scale (NOMAS) over 7 days from baseline was significantly higher in the study group infants as compared to control group (9.25 (1.73) vs 4.79 (1.52), P=0.001). Infants in the study group reached full independent wati

spoon feeds significantly earlier than the infants in control group (4.0 (0.8) d; vs 6.64 (1.0) d; P=0.001). There was significant increase in weight gain after enrolment in infants in study group compared to those in control group.

CONCLUSION:
Oral stimulation program improves the oro-motor skills and growth velocity in 28-32 week preterm infants. There is decreased transition time from gavage to full independent feeds by mouth.

Pediatr Int. 2019 Apr;61(4):388-392. doi: 10.1111/ped.13798. (Open access available)

New-generation fish oil and olive oil lipid for prevention of oxidative damage in preterm infants: Single center clinical trial at university hospital in Turkey.

Ozkan H, Koksal N, Dorum BA, Kocael F, Ozarda Y, Bozyigit C, Dogan P, Guney Varal I, Bagci O.
Turkey

BACKGROUND:
Parenteral nutrition (PN) has been widely used in preterm infants. The lipid solutions used for PN, however, are associated with oxidative stress and morbidity. The aim of this study was to compare the effectiveness of a new-generation lipid emulsion (SMOFLipid) and olive-oil based lipid emulsion for prevention of PN-associated oxidative damage.

METHODS:
Preterm infants < 32 weeks of gestational age were included in this prospective randomized study. All infants were randomized to SMOFlipid or olive-oil based lipid emulsion (ClinOleic). Lipid peroxidation products were evaluated in all infants. In addition, total antioxidant capacity (TAC), and both pro- and anti-inflammatory cytokines were studied at days 0, 7 and 14.

RESULTS:
A total of 89 infants (SMOFlipid, n = 42; ClinOleic, n = 47) were enrolled. TAC was higher in the SMOFlipid group compared with the ClinOleic group at all time points, and the difference on day 7 was statistically significant. Although the anti-inflammatory cytokine interleukin-10 was higher in the SMOFlipid group, this difference was not significant. Bronchopulmonary dysplasia (BPD) was lower in the SMOFlipid group (14.1%) than in the ClinOleic group (31.2%), but this finding was non-significant p > 0.05. The rate of severe BPD was significantly lower in the SMOFlipid group.

CONCLUSION:
To our best of knowledge, this is the first study to suggest that SMOFlipid might decrease oxidative damage and oxidative-stress-associated morbidity compared with olive oil-based emulsion in preterm infants.

Pediatr Res. 2018 Oct 18. doi: 10.1038/s41390-018-0211-9. [Epub ahead of print]

Effect of prebiotic and probiotic supplementation on neurodevelopment in preterm very low birth weight infants: findings from a meta-analysis.

Upadhyay RP, Taneja S, Chowdhury R, Strand TA, Bhandari N.
India, Norway.

BACKGROUND:
Preterm very low birth weight (VLBW) infants are at risk of gut dysbiosis and neurodevelopmental deficits. Prebiotics and probiotics may modulate gut microbiota and influence brain functions. This review synthesizes literature on effect of prebiotic and/or probiotic supplementation in preterm VLBW on their neurodevelopmental outcomes.

METHODS:
Search was done using PubMed and CENTRAL. Randomized controlled trials (RCTs) in preterm infants (<37 weeks gestation) and/or infants with birth weight <1500 g that evaluated the effect of prebiotic and/or probiotic supplementation on neurodevelopmental outcomes were included. Weighted mean difference in cognitive and motor scores; pooled relative risks for cognitive and motor impairment, cerebral palsy, hearing, and visual impairment were estimated. Quality of evidence was assessed using the GRADE criteria.

RESULTS:
Out of 275 articles identified, seven were included for review. All, except one, were done in preterms <33 weeks of gestation. Age of assessment of outcomes was ≥18-22 months of corrected age in five studies. Interventions did not decrease or increase the risk of cognitive and motor impairment, cerebral palsy, visual, and hearing impairment. Quality of evidence was "low" to "very low."

CONCLUSIONS:
Limited evidence from RCTs does not demonstrate a difference in neurodevelopmental outcomes between prebiotic/probiotic treated and untreated control groups.

J Perinatol. 2018 Oct;38(10):1324-1330. doi: 10.1038/s41372-018-0169-9. Epub 2018 Jul 27.

Standard care with plastic bag or portable thermal nest to prevent hypothermia at birth: a three-armed randomized controlled trial.

Shabeer MP, Abiramalatha T, Devakirubai D, Rebekah G, Thomas N.
India

OBJECTIVE:
To assess the efficacy of adding plastic bag or portable thermal nest (PTN) to standard care in preventing hypothermia soon after birth in 1500-2499 g infants.

METHODS:

Infants were randomized into standard thermal care alone, plastic bag with standard care or PTN with standard care. Axillary temperature was measured at admission and every 30 min till euthermia. All babies were followed-up till day 7.

RESULTS:
We recruited 300 infants: plastic bag (101), PTN (99) and standard care group (100). Admission temperature was 36.4 °C (0.52) in plastic bag group, 36.3 °C (0.50) in PTN and 36.1 °C (0.59) in standard care group ($p < 0.001$). Incidence of hypothermia was lowest in plastic bag group (44.6%), followed by PTN (60%) and standard care (67%). Secondary outcomes were comparable.

CONCLUSION:
Addition of plastic bag or PTN to standard care significantly reduces incidence and duration of hypothermia soon after birth. Plastic bag is more effective than PTN.

Pediatrics. 2019 May;143(5). pii: e20182565. doi: 10.1542/peds.2018-2565. Epub 2019 Apr 2.

Platelet Transfusion for PDA Closure in Preterm Infants: A Randomized Controlled Trial.

Kumar J, Dutta S, Sundaram V, Saini SS, Sharma RR, Varma N.
India

BACKGROUND AND OBJECTIVES:
Thrombocytopenia is associated with late closure of patent ductus arteriosus (PDA). There are few studies evaluating platelet transfusions to treat PDA. We compared **liberal platelet-transfusion criteria (to maintain a platelet count >100 000 per µL) versus standard criteria achieve earlier PDA closure among thrombocytopenic preterm neonates (<35 weeks' gestation) with hemodynamically significant PDA (hs-PDA) presenting within the first 2 weeks of life.**

METHODS:
Thrombocytopenic (<100 000 per µL) preterm neonates with hs-PDA were enrolled and randomly allocated to the liberal and standard transfusion groups: 22 in each arm. They underwent echocardiography daily until closure of PDA, completion of 120 hours follow-up, or death. **All subjects received standard cotreatment with nonsteroidal antiinflammatory drugs.** Primary outcome of time to PDA closure was compared by survival analysis. Multivariate Cox proportional hazard regression was performed with randomization group, baseline platelet count, gestational age, and age at enrollment as predictor variables.

RESULTS:
Median time to PDA closure was 72 (95% confidence interval [CI] 55.9-88.1) versus 72 (95% CI 45.5-98.4) hours in the liberal versus restrictive transfusion groups, respectively (unadjusted hazard ratio 0.88 [95% CI 0.4-1.9]; $P = .697$). Despite adjusting for potential confounders, there was no significant difference in time to PDA closure. **In the liberal transfusion group,**

41% of infants had any grade of intraventricular hemorrhage compared with 4.5% in the restrictive group (*P* = .009).

CONCLUSIONS:
Attempting to maintain a platelet count >100 000 per µL by liberally transfusing platelets in preterm thrombocytopenic neonates with hs-PDA does not hasten PDA closure.

PLoS One. 2019 Jan 31;14(1):e0211476. doi: 10.1371/journal.pone.0211476. eCollection 2019. (Open access available)

'Nasal mask' in comparison with 'nasal prongs' or 'rotation of nasal mask with nasal prongs' reduce the incidence of nasal injury in preterm neonates supported on nasal continuous positive airway pressure (nCPAP): A randomized controlled trial.

Bashir T, Murki S, Kiran S, Reddy VK, Oleti TP.
India

BACKGROUND:
With increasing use of nCPAP, the safety and comfort associated with nCPAP have come into the forefront. The reported incidence of nasal injuries associated with the use of nCPAP is 20% to 60%. A recent meta-analysis concluded that the use of nasal masks significantly decreases CPAP failure and the incidence of moderate to severe nasal injury and stress the need for a well powered RCT to confirm their findings.

METHODS:
In this Open label, 3 arms, sequential, stratified randomized controlled trial, we evaluated the incidence and severity of nasal injury at removal of nCPAP when using two different nasal interfaces and in three groups (i.e. rotation group, mask continue group, prong continue group). Preterm infants with gestation ≤ 30 weeks and respiratory distress within the first 6 hours of birth and in need of CPAP were eligible for the study.

RESULTS:
Among the 175 newborns included in the study, incidence of nasal injury in mask continue group [n = 19/57 (33.3%)] was significantly less as compared to prong continue group [n = 55/60 (91.6%)] and rotation group [33/ 58 (56.9%), p value <0.0001]. Median maximum nasal injury score was significantly less in Mask continue group as compared to Prong continue group and Rotation group [Injury Score 0 (IQR 0-1) vs. Injury Score 3 (IQR 2-5) vs. Injury Score 1 (IQR 0-2), p value = <0.0001] respectively. The proportion of infants failing nCPAP was similar across the three groups.

CONCLUSION:
nCPAP with nasal masks significantly reduces nasal injury in comparison with nasal prongs or rotation of nasal prongs and nasal masks. However, the type of interface did not affect the nCPAP failure rates.

Perinatal asphyxia

Arch Dis Child. 2019 Feb 23. pii: archdischild-2018-315805. doi: 10.1136/archdischild-2018-315805. [Epub ahead of print] (Open access available)

Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: a systematic review.

Bhatt GC, Gogia P, Bitzan M, Das RR.

OBJECTIVE:
To compare the efficacy and safety of theophylline or aminophylline for prevention of acute kidney injury (AKI) in neonates and children.

DESIGN:
Systematic review and meta-analysis with application of Grading of Recommendations, Assessment, Development and Evaluation system.

DATA SOURCES:
PubMed/MEDLINE, Embase, Google Scholar and Cochrane renal group were searched from 1970 to May 2018.

ELIGIBILITY CRITERIA:
Randomised clinical trials and quasi-randomised trials comparing the efficacy and safety of prophylactic theophylline or aminophylline for prevention of AKI in neonates and children were included. The primary outcomes were: incidence of AKI, serum creatinine levels and all-cause mortality.

RESULTS:
A total of nine trials were included in the qualitative synthesis. Six trials including 436 term neonates with birth asphyxia who received a single dose of theophylline were finally included in the meta-analysis. The pooled estimate showed 60% reduction in the incidence of AKI in neonates with severe birth asphyxia (RR: 0.40; 95% CI 0.3 to 0.54; heterogeneity: I=0%) (moderate quality evidence), decrease in serum creatinine over days 2-5 (very low to low quality evidence) without significant difference in all-cause mortality (RR: 0.88; 95% CI 0.52 to 1.50; heterogeneity: I=0%) (very low-quality evidence). A significant difference in the negative fluid balance, increase in GFR and decrease in urinary β2 microglobulin was seen in favour of theophylline.

CONCLUSION AND RELEVANCE:
A single dose of prophylactic theophylline helps in prevention of AKI/severe renal dysfunction in term neonates with severe birth asphyxia (moderate quality evidence) without increasing the risk of complications and without affecting all-cause mortality (very low-quality evidence).

J Perinatol. 2018 Nov;38(11):1512-1517. doi: 10.1038/s41372-018-0223-7. Epub 2018 Sep 11. (Open access available)

Does fluid restriction improve outcomes in infants with hypoxic ischemic encephalopathy? A pilot randomized controlled trial.

Tanigasalam V, Plakkal N, Vishnu Bhat B, Chinnakali P.
India

OBJECTIVE:
To evaluate whether a strategy of restricted fluid intake in the first 4 days reduces mortality and morbidity among term neonates with moderate to severe hypoxic ischemic encephalopathy (HIE) treated with therapeutic hypothermia.

STUDY DESIGN:
Eighty neonates with HIE were randomized between January 2016 and February 2018 to receive normal fluid intake (n = 40) or restricted fluid intake (two-third of normal intake; n = 40) in the first 4 days of life. The primary outcome was a composite of death or major neurodevelopmental disability at 6 months of age.

RESULTS:
The primary outcome occurred in 10 infants (26%) in the fluid-restricted group and 3 infants (8%) in the normal fluid intake group, but the difference was not statistically significant (p = 0.065). Five infants in the fluid-restricted group had hypoglycemia (p = 0.055).

CONCLUSION:
Restricted fluid intake did not reduce the composite outcome of death or neurodevelopmental disability and was associated with a trend toward more hypoglycemia.

J Neonatal Perinatal Med. 2018;11(4):393-397. doi: 10.3233/NPM-17154. (Open access available)

Gastric lavage in babies born through meconium stained amniotic fluid in prevention of early feed intolerance: A randomized controlled trial.

Yadav SK, Venkatnarayan K, Adhikari KM, Sinha R, Mathai SS.
Nepal, India

OBJECTIVE:
To evaluate the efficacy of gastric lavage (GL) in preventing feed intolerance in babies born through Meconium stained amniotic fluid (MSAF).

STUDY DESIGN:
In this randomized trial conducted at a tertiary care hospital, neonates born of **MSAF after 34 weeks period of gestation requiring routine care were randomly allocated to GL with**

10 ml/kg of normal saline. The control group did not receive GL. The subjects were monitored for first 24 hours in predefined time epochs. The primary outcome was incidence of feed intolerance which was defined as vomiting or abdominal distension more than 2 cm from baseline measure. Babies were also monitored for potential adverse events due to GL and total duration of hospital stay.

RESULTS:
Baseline parameters were comparable. The incidence of feed intolerance was not significant in the GL group [4.6% vs 9.2%; RR 0.92 (0.29-3)]. There were no adverse events secondary to GL. The duration of hospital stay was comparable between groups.

CONCLUSION:
GL in neonates born of MSAF does not reduce feed intolerance.

Neonatal infection

Zhongguo Dang Dai Er Ke Za Zhi. 2019 Apr;21(4):327-331. (Open access available)

Clinical effect of exogenous pulmonary surfactant in the treatment of severe neonatal infectious pneumonia: a multicenter prospective clinical trial

Qiu RX, Liu X, Wang JL, Cai C, Zeng JA, Liu HC, Cheng R, Li ZK, Liu J.
China

OBJECTIVE:
To study the clinical effect of calsurf, a domestic exogenous pulmonary surfactant, in the treatment of severe neonatal infectious pneumonia.

METHODS:
A total of 208 neonates with severe infectious pneumonia who hospitalized in 5 hospitals of China were enrolled. According to their parents' wishes on admission, these neonates were administered with conventional treatment (control group; n=81) and calsurf treatment + conventional treatment (calsurf treatment group, n=127). The two groups were compared in terms of the degree of oxygen dependence on admission, blood gas parameters before and after treatment, lung ultrasound results, duration of mechanical ventilation, length of hospital stay, hospital costs, complications and prognosis.

RESULTS:
Compared with the control group on admission, the calsurf treatment group had significantly higher inhaled oxygen concentration and partial pressure of carbon dioxide and significantly lower arterial partial pressure of oxygen and oxygenation index ($P<0.01$). After 1 hour of treatment, both groups had significant improvements in the above indices ($P<0.05$), and the improvements were more significant in the calsurf treatment group ($P<0.05$). After 4-6 hours of calsurf administration, there was a significant reduction in the degree of pulmonary consolidation. The calsurf treatment group had significantly shorter duration of

mechanical ventilation and length of hospital stay than the control group, while there was no significant difference in the incidence rate of complications between the two groups. The neonates of both groups had a good prognosis.

CONCLUSIONS:
In neonates with severe infectious pneumonia, calsurf treatment can significantly improve oxygenation, reduce the degree of pulmonary consolidation, and shorten the duration of mechanical ventilation and length of hospital stay. Therefore, it should be considered in neonates with severe infectious pneumonia.

Cochrane Database Syst Rev. 2019 Apr 11;4:CD007646. doi: 10.1002/14651858.CD007646.pub3. (Open access available)

Community-based antibiotic delivery for possible serious bacterial infections in neonates in low- and middle-income countries.

Duby J, Lassi ZS, Bhutta ZA.

BACKGROUND:
The recommended management for neonates with a possible serious bacterial infection (PSBI) is hospitalisation and treatment with intravenous antibiotics, such as ampicillin plus gentamicin. However, hospitalisation is often not feasible for neonates in low- and middle-incomecountries (LMICs). Therefore, alternative options for the management of neonatal PSBI in LMICs needs to be evaluated.

OBJECTIVES:
To assess the effects of community-based antibiotics for neonatal PSBI in LMICs on neonatal mortality and to assess whether the effects of community-based antibiotics for neonatal PSBI differ according to the antibiotic regimen administered.

SEARCH METHODS:
We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 3), MEDLINE via PubMed (1966 to 16 April 2018), Embase (1980 to 16 April 2018), and CINAHL (1982 to 16 April 2018). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-randomised trials.

SELECTION CRITERIA:
We included randomised, quasi-randomised and cluster-randomised trials. For the first comparison, we included trials that compared antibiotics which were initiated and completed in the community to the standard hospital referral for neonatal PSBI in LMICs. For the second comparison, we included trials that compared simplified antibiotic regimens which relied more on oral antibiotics than intravenous antibiotics to the standard regimen of seven to 10 days of injectable penicillin/ampicillin with an injectable aminoglycoside delivered in the community to treat neonatal PSBI.
DATA COLLECTION AND ANALYSIS:

We extracted data using the standard methods of the Cochrane Neonatal Group. The primary outcomes were all-cause neonatal mortality and sepsis-specific neonatalmortality. We used the GRADE approach to assess the quality of evidence.

MAIN RESULTS:
For the first comparison, five studies met the inclusion criteria. Community-based antibiotic delivery for neonatal PSBI reduced neonatal mortality when compared to hospital referral only (typical risk ratio (RR) 0.82, 95% confidence interval (CI) 0.68 to 0.99; 5 studies, n = 125,134; low-quality evidence). There was, however, a high level of statistical heterogeneity (I^2 = 87%) likely, due to the heterogenous nature of the study settings as well as the fact that four of the studies provided various co-interventions in conjunction with community-based antibiotics. Community-based antibiotic delivery for neonatal PSBI showed a possible effect on reducing sepsis-specific neonatal mortality (typical RR 0.78, 95% CI 0.60 to 1.00; 2 studies, n = 40,233; low-quality evidence).
For the second comparison, five studies met the inclusion criteria. Using a simplified antibiotic approach resulted in similar rates of neonatal mortality when compared to the standard regimen of seven days of injectable procaine benzylpenicillin and injectable procaine benzylpenicillin and injectable gentamicin delivered in community-settings for neonatal PSBI (typical RR 0.81, 95% CI 0.44 to 1.50; 3 studies, n = 3476; moderate-quality evidence). In subgroup analysis, the simplified antibiotic regimen of seven days of oral amoxicillin and injectable gentamicin showed no difference in neonatal mortality (typical RR 0.84, 95% CI 0.47 to 1.51; 3 studies, n = 2001; moderate-quality evidence). Two days of injectable benzylpenicillin and injectable gentamicin followed by five days of oral amoxicillin showed no difference in neonatal mortality (typical RR 0.88, 95% CI 0.29 to 2.65; 3 studies, n = 2036; low-quality evidence). Two days of injectable gentamicin and oral amoxicillin followed by five days of oral amoxicillin showed no difference in neonatal mortality (RR 0.67, 95% CI 0.24 to 1.85; 1 study, n = 893; moderate-quality evidence). For fast breathing alone, seven days of oral amoxicillin resulted in no difference in neonatal mortality (RR 0.99, 95% CI 0.20 to 4.91; 1 study, n = 1406; low-quality evidence). None of the studies in the second comparison reported the effect of a simplified antibiotic regimen on sepsis-specific neonatal mortality.

AUTHORS' CONCLUSIONS:
Low-quality data demonstrated that community-based antibiotics reduced neonatal mortality when compared to the standard hospital referral for neonatal PSBI in resource-limited settings. The use of co-interventions, however, prevent disentanglement of the contribution from community-based antibiotics. Moderate-quality evidence showed that simplified, community-based treatment of PSBI using regimens which rely on the combination of oral and injectable antibiotics did not result in increased neonatal mortality when compared to the standard treatment of using only injectable antibiotics. Overall, the evidence suggests that simplified, community-based antibiotics may be efficacious to treat neonatal PSBI when hospitalisation is not feasible. However, implementation research is recommended to study the effectiveness and scale-up of simplified, community-based antibiotics in resource-limited settings.

Jaundice

Lancet Glob Health. 2018 Oct;6(10):e1122-e1131. doi: 10.1016/S2214-109X(18)30373-5. Epub 2018 Aug 28. (Open access available)

Filtered sunlight versus intensive electric powered phototherapy in moderate-to-severe neonatal hyperbilirubinaemia: a randomised controlled non-inferiority trial.

Slusher TM, Vreman HJ, Brearley AM, Vaucher YE, Wong RJ, Stevenson DK, Adeleke OT, Ojo IP, Edowhorhu G, Lund TC, Gbadero DA.
Nigeria, USA,

BACKGROUND:
Kernicterus resulting from severe neonatal hyperbilirubinaemia is a leading cause of preventable deaths and disabilities in low-income and middle-income countries, partly because high-quality intensive phototherapy is unavailable. Previously, we showed that filtered-sunlight phototherapy (FSPT) was efficacious and safe for treatment of mild-to-moderate neonatal hyperbilirubinaemia. We aimed to extend these studies to infants with moderate-to-severe hyperbilirubinaemia.

METHODS:
We did a prospective, randomised controlled non-inferiority trial in Ogbomoso, Nigeria-a simulated rural setting. Near-term or term infants aged 14 days or younger who were of 35 weeks or more gestational age and with total serum bilirubin concentrations at or above the recommended age-dependent treatment levels for high-risk neonates were **randomly assigned (1:1) to either FSPT or intensive electric phototherapy (IEPT).** Randomisation was computer-generated, and neither clinicians nor the parents or guardians of participants were masked to group allocation. FSPT was delivered in a transparent polycarbonate room lined with **commercial tinting films that transmitted effective phototherapeutic light, blocked ultraviolet light, and reduced infrared radiation**. The primary outcome was efficacy, which was based on assessable treatment days only (ie, those on which at least 4 h of phototherapy was delivered) and defined as a rate of increase in total serum bilirubin concentrations of less than 3·4 μmol/L/h in infants aged 72 h or younger, or a decrease in total serum bilirubin concentrations in those older than 72 h. **Safety was defined as no sustained hypothermia, hyperthermia, dehydration, or sunburn and was based on all treatment days.** Analysis was by intention to treat with a non-inferiority margin of 10%.

FINDINGS:
174 neonates were enrolled and randomly assigned: 87 to FSPT and 87 to IEPT. Neonates in the FSPT group received 215 days of phototherapy, 82 (38%) of which were not assessable. Neonates in the IEPT group received 219 treatment days of phototherapy, 67 (31%) of which were not assessable. Median irradiance was 37·3 μW/cm/nm (IQR 21·4-56·4) in the FSPT group and 50·4 μW/cm/nm (44·5-66·2) in the IEPT group. FSPT was efficacious on 116 (87·2%) of 133 treatment days; IEPT was efficacious on 135 (88·8%) of 152 treatment days (mean difference -1·6%, 95% CI -9·9 to 6·7; p=0·8165). Because the CI did not extend below -10%, we concluded that FSPT was not inferior to IEPT. Treatment was safe for all neonates.

INTERPRETATION:
FSPT is safe and no less efficacious than IEPT for treatment of moderate-to-severe neonatal hyperbilirubinaemia in near-term and term infants.

J Obstet Gynecol Neonatal Nurs. 2018 Nov;47(6):795-802. doi: 10.1016/j.jogn.2018.07.008. Epub 2018 Aug 30.

Systematic Review of the Effect of Reflective Materials Around a Phototherapy Unit on Bilirubin Reduction Among Neonates With Physiologic Jaundice in Developing Countries.

Lee Wan Fei S, Chew KS, Pawi S, Chong LT, Abdullah KL, Lim LT, Rintika F.

OBJECTIVE:
To identify the efficacy and safety of the use of various cost-effective reflective materials around phototherapy units to reduce the duration of phototherapy and hasten the reduction of bilirubin among neonates with physiologic jaundice.

DATA SOURCES:
A systematic review of randomized controlled trials identified from searches in the Cumulative Index to Nursing and Allied Health Literature, ScienceDirect, Embase, and the Cochrane Library with the use of keywords, MeSH terms, operators, and the review of reference lists of retrieved articles.

STUDY SELECTION:
From a total of 186 studies initially screened, five were eventually included in this analysis.

DATA EXTRACTION:
Two authors independently reviewed each study with a standard template. Review parameters included the quality of each study based on the Physiotherapy Evidence Database scale and the Consolidated Standards of Reporting Trials guidelines.

DATA SYNTHESIS:
All studies were generalizable and were rated as high quality on the Physiotherapy Evidence Database scale; one study scored 8 points, and the other four scored 6 points each. The reflective materials used in these studies included the following: white 100% cotton cloths (one study), white plastic covers (two studies), underpads (one study), and silver fabric cloth (one study). **Pooled analysis of three studies indicated that reflective materials significantly reduced the duration of phototherapy with a large effect size of 0.82 (p = .04).** Pooled analysis of another three studies indicated that the mean decrease of the total serum bilirubin 4 hours after the initiation of phototherapy was significantly greater when reflective materials were added (mean difference of 11.39 μmol/L, 95% confidence interval [2.26, 20.52 μmol/L], p = .01).
CONCLUSION:

The addition of reflective materials to phototherapy units may be therapeutic for neonates with physiologic jaundice.

Nutrition

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Growth monitoring

Micronutients, multivitamins, and food fortification

(See also Vitamin A)

PLoS One. 2019 Feb 13;14(2):e0211693. doi: 10.1371/journal.pone.0211693. eCollection 2019.
(Open access available)

Multiple micronutrient supplementation using spirulina platensis and infant growth, morbidity, and motor development: Evidence from a randomized trial in Zambia.

Masuda K, Chitundu M.
Tokyo, Zambia

Abstract
In developing countries, micronutrient deficiency in infants is associated with growth faltering, morbidity, and delayed motor development. One of the potentially low-cost and sustainable solutions is to use locally producible food for the home fortification of complementary foods. This study aimed to test the hypothesis that **locally producible spirulina platensis** supplementation would achieve the following: 1) increase infant physical growth, 2) reduce morbidity, and 3) improve motor development. **We randomly assigned 501 Zambian infants into the control group or the spirulina group. Children in the control group (n = 250) received a soya-maize-based porridge for 12 months; those in the spirulina group (n = 251) received the same food with the addition of spirulina.** We assessed the change in infants' anthropometric status, morbidity (probable pneumonia, cough, probable malaria, and fever), and motor development over 12 months. The baseline characteristics were not different between the two groups. The attrition rate (47/501) was low. The physical growth of infants in the two groups was similar at 12 months of intervention, as measured by height-for-age z-scores and weight-for-age z-scores. Infants in the spirulina group were 11 percentage points less likely to develop a cough (CI: -0.23, -0.00; $P < 0.05$) and were more likely to be able to walk alone at 15 months (0.96 ± 0.19) than infants in the control group (0.92 ± 0.28). Home-fortification of complementary foods using spirulina

had positive effects on upper respiratory infection morbidity prevention and motor milestone acquisition among Zambian infants.

Nutr J. 2018 Sep 15;17(1):86. doi: 10.1186/s12937-018-0391-5. (Open access available)

Efficacy of high zinc biofortified wheat in improvement of micronutrient status, and prevention of morbidity among preschool children and women - a double masked, randomized, controlled trial.

Sazawal S, Dhingra U, Dhingra P, Dutta A, Deb S, Kumar J, Devi P, Prakash A.
India, USA

BACKGROUND:
Biofortification of staple food crops with zinc (Zn) can be one of the cost-effective and sustainable strategies to combat zinc deficiency and prevent morbidity among the target population. Agronomic approaches such as application of Zn fertilizers to soil and/or foliar spray seem to be a practical tool for Zn biofortification of wheat. However, there is a need to evaluate its efficacy from randomized controlled trials. This study aimed to **evaluate the efficacy of zinc biofortified wheat flour on zinc status and its impact on morbidity among children aged 4-6 years and non-pregnant non lactating woman of child bearing age (WCBA) in Delhi, India.**

METHODS:
In a community based, double-masked randomized controlled trial, 6005 participants (WCBA and child pairs) were enrolled and randomly allocated to receive either high zinc biofortified wheat flour (HZn, 30 ppm zinc daily) or low zinc biofortified wheat flour (LZn, 20 ppm zinc daily) for 6 months (WCBA @ 360 g/day and children @ 120 g/day). Baseline and endline blood samples were obtained for assessing hematological markers; zinc status and data on compliance and morbidity were collected.

RESULTS:
Compliance rates were high; ~ 88% of the WCBAs in both the groups consumed 50% or more of recommended amount of biofortfied wheat flour during the follow up. Similarly 86.9% children in HZn and 87.5% in LZn consumed 50% or more of recommended wheat flour intake. **There was no significant difference in mean zinc levels between the groups at end study. This observation might be due to a marginal difference in zinc content (10 ppm) between the HZn and LZn wheat flour, and a short intervention period.** However a positive impact of bio-fortification on self-reported morbidity was observed. **Compared to children in LZn group, children in HZn group had 17% (95% CI: 6 to 31%, p = 0.05) and 40% (95% CI: 16 to 57%; p = 0.0019) reduction in days with pneumonia and vomiting respectively**. WCBA in the HZn group also showed a statistically significant 9% fewer days with fever compared to LZn group.

CONCLUSIONS:
Biofortified wheat flour had a good compliance among children and WCBAs. Significant improvement on some of the self-reported morbidity indicators suggests that evaluating

longer-term effects of biofortification with higher grain zinc content would be more appropriate.

Nutrients. 2018 Oct 15;10(10). pii: E1508. doi: 10.3390/nu10101508. (Open access available)
Effectiveness of a Program Intervention with Reduced-Iron Multiple Micronutrient Powders on Iron Status, Morbidity and Growth in Young Children in Ethiopia.
Samuel A, Brouwer ID, Feskens EJM, Adish A, Kebede A, De-Regil LM, Osendarp SJM.
Ethiopia, The Netherlands, Canada

Abstract
Despite the potential for improving iron status and child growth in low- and middle-income settings, concerns on the safety of high iron dosages of Micronutrient Powders (MNP currently limit their applicability in programs. We examined the effectiveness and risks of an integrated complementary feeding program with low iron dose (6 mg/serving) MNP among 6⁻23-month-old Ethiopian children using a quasi-experimental study design comparing children from five intervention districts (*n* = 1172) to those from four matched non-intervention districts (*n* = 1137). Haemoglobin concentrations increased in intervention and decreased in non-intervention children (group-difference +3.17 g/L), but without improvement in iron stores. **Intervention children were 2.31 times more likely to have diarrhoea and 2.08 times more likely to have common cold and flu, but these differences decreased towards the end of the intervention**. At end line, intervention children had higher mean Height-for-Age Zscore (HAZ) and a 51% reduced odds of being stunted compared to non-intervention children. MNP with low iron dose, when provided combined with other Infant and Young Child Feeding (IYCF) interventions, marginally improved haemoglobin status and resulted in a remarkable improvement in linear growth in 6-23 month-old children. These benefits likely outweigh the relatively small increase in the risk of diarrhoea.

J Nutr. 2018 Sep 1;148(9):1462-1471. doi: 10.1093/jn/nxy113. (Open access available)
Cognitive Performance in Indian School-Going Adolescents Is Positively Affected by Consumption of Iron-Biofortified Pearl Millet: A 6-Month Randomized Controlled Efficacy Trial.
Scott SP, Murray-Kolb LE, Wenger MJ, Udipi SA, Ghugre PS, Boy E, Haas JD.
USA, India

BACKGROUND:
Iron deficiency remains the most prevalent micronutrient deficiency globally, but few studies have examined how iron status relates to cognition in adolescents. Iron biofortification of staple food crops is being scaled up, yet it is unknown whether consuming biofortified crops can benefit cognition.

Objective:

Our objective was to determine the efficacy of iron-biofortified pearl millet in improving attention and memory in Indian school-going adolescents.

Methods:
A double-blind, randomized, intervention study was conducted in 140 Indian boys and girls, aged 12-16 y, who were assigned to consume iron-biofortified [Fe = 86 parts per million (ppm)] or conventional (Fe = 21-52 ppm) pearl millet. Hemoglobin, ferritin, and transferrin receptor (TfR) were measured and body iron (BI) was calculated at baseline and after 4 and 6 mo. Five measures of cognitive function were obtained at baseline and 6 mo: simple reaction time (SRT), Go/No-Go (GNG) task, Attentional Network Task (ANT), Composite Face Effect (CFE) task, and Cued Recognition Task (CRT). Intention-to-treat analysis was used.

Results:
Daily iron intake from pearl millet was higher in those consuming biofortified compared with conventional pearl millet (19.6 compared with 4.8 mg/d). Effects on ferritin, TfR, and BI at 4 mo, and on TfR at 6 mo (all $P < 0.05$), indicated efficacy of biofortified pearl millet over conventional pearl millet in improving iron status. **Compared with conventional pearl millet, the consumption of biofortified pearl millet resulted in greater improvement in attention (SRT, GNG, and ANT) and memory (CFE and CRT). Reaction time decreased twice as much from 0 to 6 mo in those consuming biofortified compared with conventional pearl millet on attention tasks (SRT: -123 compared with -63 ms; GNG: -67 compared with -30 ms; ANT double cue: -74 compared with -32 ms; all $P < 0.01$).**

Conclusion:
Consuming iron-biofortified pearl millet improves iron status and some measures of cognitive performance in Indian adolescents.

Nutr J. 2018 Aug 13;17(1):76. doi: 10.1186/s12937-018-0385-3. (Open access available)

Fortified food supplementation in children with reduced dietary energy and micronutrients intake in Southern Mexico.

Añorve-Valdez G, Quezada-Sánchez AD, Mejía-Rodríguez F, García-Guerra A, Neufeld LM.
Mexico, Switzerland

BACKGROUND:
Nutritional supplements are an important source of complementary food for young children, since they may either complement or substitute nutrients obtained from other food sources. Assessing how the introduction of different types of supplements modifies the consumption of other food sources may help in designing supplementation programs that aim to improve the nutrition of vulnerable populations. The objetive is to quantify dietary energy and nutrient intake among children aged 6-12 months who received one of three nutritional supplements.

METHODS:

A cluster-randomized trial was conducted from 2005 to 2007. Urban communities were randomly allocated to one of three intervention groups receiving one of the following: a milk-based fortified food, micronutrient powders, or syrup. Each supplement was fortified with equal amounts of micronutrients. Dietary intake was estimated using a food frequency questionnaire (FFQ) to reflect the average consumption over the month prior to the interview. Children between 6 and 12 months of age were recruited. Median regression was performed with adjusted standard errors for clustered data, and the linear predictors for the median included the study group, study stage and their interaction. Adjusted medians by study group and study stage were obtained as post-estimations.

RESULTS:
No statistically significant differences between study groups were observed at baseline. After four months of supplementation, the children in the fortified food group had a smaller increase in median dietary energy (183.7 kcal, CI95%: 59.9, 307.5) and dietary protein (6.6 g, CI95%: 2.6, 10.6) intake from their home diet than those in the syrup group ($p < 0.05$). These differences remained significant after adjusting for group differences at baseline. Regarding covariate-adjusted median changes from baseline to follow-up at 10 months, the children in the fortified food group had a smaller median increase in dietary energy intake than those in the syrup group (698 vs 915 kcal), with a difference of 217.9 kcal (CI95%: 20.4, 415.4).

CONCLUSION:
Children in the fortified food group consumed less dietary energy, protein, and micronutrients than those in the micronutrient powder and syrup groups. It is possible that absolute nutrient intake may be overestimated by the FFQ, but this possibility does not compromise the ability to compare study groups. Given the observed differences in dietary energy consumption among the three supplemented groups, it can be concluded that supplementation with micronutrient powders is an adequate option for urban children who have met their minimum energy and protein requirements.

Nutrients. 2018 Oct 1;10(10). pii: E1394. doi: 10.3390/nu10101394. (Open access available)

A Combined Dietary and Cognitive Intervention in 3⁻5-Year-Old Children in Indonesia: A Randomized Controlled Trial.

Schneider N, Geiser E, Gosoniu LM, Wibowo Y, Gentile-Rapinett G, Tedjasaputra MS, Sastroasmoro S.
Switzerland, Indonesia

Abstract
Early childhood nutritional interventions typically combine nutritional and psychosocial stimulation. Such combined interventions result in long-lasting improvements of cognitive abilities in children who are malnourished. Here, we investigated potential cognitive abilities in normally developing children in Indonesia who were, however, at risk for suboptimal cognitive development due to little psychosocial stimulation in their home environment. **In a randomized controlled intervention, children of the experimental group received nutritional supplementation combined with cognitive stimulation.** Pre- and post-

intervention measurements included cognitive development and functioning, behavior, and mother¯child interaction. **The experimental and control group received nutritional supplementation in the form of a fortified or unfortified milk powder, respectively.** Additionally, the children and parents of the experimental group jointly engaged in daily learning activities at home and performed iPad-based tasks designed to foster cognitive abilities. The experimental group compared to the control group displayed a significantly higher increase in intelligence quotient as well as a significantly larger reduction in attentional problems after the intervention. These results indicate that low-level cognitive stimulation in combination with nutritional supplementation during early childhood can be an effective intervention that improves global cognitive functioning in healthy developing children.

PLoS One. 2019 Jan 23;14(1):e0210899. doi: 10.1371/journal.pone.0210899. eCollection 2019. (Open access available)

Health effects of micronutrient fortified dairy products and cereal food for children and adolescents: A systematic review.

Eichler K, Hess S, Twerenbold C, Sabatier M, Meier F, Wieser S.
Switzerland.

Abstract
INTRODUCTION:
Micronutrient (MN) deficiencies cause a considerable burden of disease for children in many countries. Dairy products or cereals are an important food component during adolescence. Fortification of dairy products or cereals with MN may be an effective strategy to overcome MN deficiencies, but their specific impact on health in this age group is poorly documented.

METHODS:
We performed a systematic review and meta-analysis (registration number CRD42016039554) to assess the impact of MN fortified dairy products and cereal food on the health of children and adolescents (aged 5-15 years) compared with non-fortified food. We reviewed randomised controlled trials (RCT) using electronic databases (MEDLINE, EMBASE, Cochrane library; latest search: January 2018), reference list screening and citation searches. Three pairs of reviewers assessed 2048 studies for eligibility and extracted data. We assessed the risk of bias and applied GRADE to rate quality of evidence.

RESULTS:
We included 24 RCT (often multi MN fortification) with 30 pair-wise comparisons mainly from low- and middle income countries. A very small and non-significant increase of haemoglobin values emerged (0.09 g/dl [95%-CI: -0.01 to 0.18]; 13 RCT with iron fortification; very low quality of evidence). No significant difference was found on anaemia risk (risk ratio 0.87 [95%-CI: 0.76 to 1.01]; 12 RCT; very low quality), but a significant difference in iron deficiency anaemia favouring fortified food was found (risk ratio 0.38 [95%-CI: 0.18 to 0.81]; 5 RCT; very low quality). Similar effects were seen for fortified dairy products and cereals and different fortification strategies (mono- vs. dual- vs. multi-MN). Follow-up periods were often short

and the impact on anthropometric measures was weak (low quality of evidence) Very low quality of evidence emerged for the improvement of cognitive performance, functional measures and morbidity.

CONCLUSIONS:
Fortification of dairy products and cereal food had only marginal health effects in our sample population from 5-15 years. Further evidence is needed to better understand the health impact of fortified dairy products and cereals in this age group.

SYSTEMATIC REVIEW REGISTRATION:
The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 26 May 2016 (registration number CRD42016039554).

Eur J Clin Nutr. 2019 Feb 4. doi: 10.1038/s41430-019-0403-3. [Epub ahead of print] (Open access available)

Effect of antenatal and infant micronutrient supplementation on middle childhood and early adolescent development outcomes in Tanzania.

Sudfeld CR, Manji KP, Darling AM, Kisenge R, Kvestad I, Hysing M, Belinger DC, Strand TA, Duggan CP, Fawzi WW.

BACKGROUND:
There is growing evidence that nutritional interventions in the first 1000 days of life may influence long-term health and development outcomes. Few studies have examined the effect of maternal and infant micronutrient supplementation on development outcomes in sub-Saharan Africa.

METHODS:
We conducted a follow-up study of two randomized trials of antenatal and infant micronutrient supplementation conducted in Dar es Salaam, Tanzania. **We assessed the effect of maternal multiple micronutrient (MMN) supplementation in pregnancy on development of children at 11-14 years of age.** We also examined the effect of infant zinc and MMN supplementation on development at 6-8 years of age. We used generalized linear models to assess standardized mean differences (SMDs) in general intelligence, executive function, and mental health scores.

RESULTS:
We followed up 446 children whose mothers were enrolled in the maternal MMN supplementation trial and 365 children who were enrolled in the infant zinc and MMN supplementation trial. **We found no effect of maternal MMN supplementation on general intelligence (SMD: -0.03; 95% CI: -0.15, 0.09), executive function (SMD: 0.00; 95% CI: -0.11, 0.11), and mental health scores (SMD: 0.06; 95% CI: 10.10, 0.22).** We also found no effect of either infant zinc or MMN supplementation on any of the three development domains (p-values > 0.05).

CONCLUSIONS:
We found that antenatal MMN supplementation and infant zinc and MMN supplementation did not have a large effect on development outcomes in middle childhood and early adolescence in Tanzania.

Cochrane Database Syst Rev. 2019 May 10;5:CD010068. doi: 10.1002/14651858.CD010068.pub2. [Epub ahead of print] (Open access available)

Fortification of staple foods with vitamin A for vitamin A deficiency.

Hombali AS, Solon JA, Venkatesh BT, Nair NS, Peña-Rosas JP.

BACKGROUND:
Vitamin A deficiency is a significant public health problem in many low- and middle-income countries, especially affecting young children, women of reproductive age, and pregnant women. Fortification of staple foods with vitamin A has been used to increase vitamin A consumption among these groups.

OBJECTIVES:
To assess the effects of fortifying staple foods with vitamin A for reducing vitamin A deficiency and improving health-related outcomes in the general population older than two years of age.

SEARCH METHODS:
We searched the following international databases with no language or date restrictions: Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6) in the Cochrane Library; MEDLINE and MEDLINE In Process OVID; Embase OVID; CINAHL Ebsco; Web of Science (ISI) SCI, SSCI, CPCI-exp and CPCI-SSH; BIOSIS (ISI); POPLINE; Bibliomap; TRoPHI; ASSIA (Proquest); IBECS; SCIELO; Global Index Medicus - AFRO and EMRO; LILACS; PAHO; WHOLIS; WPRO; IMSEAR; IndMED; and Native Health Research Database. We also searched clinicaltrials.gov and the International Clinical Trials Registry Platform to identify ongoing and unpublished studies. The date of the last search was 19 July 2018.

SELECTION CRITERIA:
We included individually or cluster-randomised controlled trials (RCTs) in this review. The intervention included fortification of staple foods (sugar, edible oils, edible fats, maize flour or corn meal, wheat flour, milk and dairy products, and condiments and seasonings) with vitamin A alone or in combination with other vitamins and minerals. We included the general population older than two years of age (including pregnant and lactating women) from any country.

DATA COLLECTION AND ANALYSIS:

Two authors independently screened and assessed eligibility of studies for inclusion, extracted data from included studies and assessed their risk of bias. We used standard Cochrane methodology to carry out the review.

MAIN RESULTS:
We included 10 randomised controlled trials involving 4455 participants. All the studies were conducted in low- and upper-middle income countries where vitamin A deficiency was a public health issue. One of the included trials did not contribute data to the outcomes of interest.Three trials compared provision of staple foods fortified with vitamin A versus unfortified staple food, five trials compared provision of staple foods fortified with vitamin A plus other micronutrients versus unfortified staple foods, and two trials compared provision of staple foods fortified with vitamin A plus other micronutrients versus no intervention. No studies compared staple foods fortified with vitamin A alone versus no intervention.The duration of interventions ranged from three to nine months. We assessed six studies at high risk of bias overall. Government organisations, non-governmental organisations, the private sector, and academic institutions funded the included studies; funding source does not appear to have distorted the results.Staple food fortified with vitamin A versus unfortified staple food We are uncertain whether fortifying staple foods with vitamin A alone makes little or no difference for serum retinol concentration (mean difference (MD) 0.03 µmol/L, 95% CI -0.06 to 0.12; 3 studies, 1829 participants; I^2 = 90%, very low-certainty evidence). It is uncertain whether vitamin A alone reduces the risk of subclinical vitamin A deficiency (risk ratio (RR) 0.45, 95% CI 0.19 to 1.05; 2 studies; 993 participants; I^2 = 33%, very low-certainty evidence). The certainty of the evidence was mainly affected by risk of bias, imprecision and inconsistency.It is uncertain whether vitamin A fortification reduces clinical vitamin A deficiency, defined as night blindness (RR 0.11, 95% CI 0.01 to 1.98; 1 study, 581 participants, very low-certainty evidence). The certainty of the evidence was mainly affected by imprecision, inconsistency, and risk of bias.Staple foods fortified with vitamin A versus no intervention No studies provided data for this comparison.Staple foods fortified with vitamin A plus other micronutrients versus same unfortified staple foods: Fortifying staple foods with vitamin A plus other micronutrients may not increase the serum retinol concentration (MD 0.08 µmol/L, 95% CI -0.06 to 0.22; 4 studies; 1009 participants; I^2 = 95%, low-certainty evidence). The certainty of the evidence was mainly affected by serious inconsistency and risk of bias.In comparison to unfortified staple foods, fortification with vitamin A plus other micronutrients probably reduces the risk of subclinical vitamin A deficiency (RR 0.27, 95% CI 0.16 to 0.49; 3 studies; 923 participants; I^2 = 0%; moderate-certainty evidence). The certainty of the evidence was mainly affected by serious risk of bias.Staple foods fortified with vitamin A plus other micronutrients versus no intervention
Fortification of staple foods with vitamin A plus other micronutrients may increase serum retinol concentration (MD 0.22 µmol/L, 95% CI 0.15 to 0.30; 2 studies; 318 participants; I^2 = 0%; low-certainty evidence). When compared to no intervention, it is uncertain whether the intervention reduces the risk of subclinical vitamin A deficiency (RR 0.71, 95% CI 0.52 to 0.98; 2 studies; 318 participants; I^2 = 0%; very low-certainty evidence) . The certainty of the evidence was affected mainly by serious imprecision and risk of bias. No trials reported on the outcomes of all-cause morbidity, all-cause mortality, adverse effects, food intake, congenital anomalies (for pregnant women), or breast milk concentration (for lactating women).

AUTHORS' CONCLUSIONS:
Fortifying staple foods with vitamin A alone may make little or no difference to serum retinol concentrations or the risk of subclinical vitamin A deficiency. In comparison with provision of unfortified foods, provision of staple foods fortified with vitamin A plus other micronutrients may not increase serum retinol concentration but probably reduces the risk of subclinical vitamin A deficiency. Compared to no intervention, staple foods fortified with vitamin A plus other micronutrients may increase serum retinol concentration, although it is uncertain whether the intervention reduces the risk of subclinical vitamin A deficiency as the certainty of the evidence has been assessed as very low. It was not possible to estimate the effect of staple food fortification on outcomes such as mortality, morbidity, adverse effects, congenital anomalies, or breast milk vitamin A, as no trials included these outcomes. The type of funding source for the studies did not appear to distort the results from the analysis.

Eur J Clin Nutr. 2019 Apr 25. doi: 10.1038/s41430-019-0428-7. [Epub ahead of print]

Factors associated with plasma n-3 and n-6 polyunsaturated fatty acid levels in Tanzanian infants.

Kamenju P, Hertzmark E, Kabagambe EK, Smith ER, Muhihi A, Noor RA, Mshamu S, Briegleb C, Sudfeld C, Masanja H, Fawzi WW.

BACKGROUND/OBJECTIVES:
To identify factors associated with plasma polyunsaturated fatty acid (PUFA) levels among 3-month-old Tanzanian infants.

SUBJECTS/METHODS:
Infants (n = 238) and mothers (n = 193) randomly selected from participants in the neonatal vitamin A supplementation randomized controlled trial. A cross-sectional study of maternal-infant pairs at 3 months postpartum.

RESULTS:
All infant total, n-3, n-6, and individual PUFA levels were correlated with maternal levels. Infant plasma n-3 PUFA levels were higher when maternal n-3 PUFA levels were higher (mean difference in infant % fatty acid per unit increase in maternal levels ± standard error: 0.79 ± 0.08; P < 0.01). Infant plasma docosahexaenoic acid (DHA) levels were positively associated with maternal DHA levels (0.77 ± 0.09; P < 0.01) but were lower for twin births (-0.55 ± 0.27; P = 0.03). Greater birth weight in kilograms (1.00 ± 0.43; P = 0.02) and higher maternal n-6 PUFA levels (0.20 ± 0.07; P < 0.01) were positively associated with higher infant n-6 PUFA levels, whereas maternal mono-unsaturated fatty acid (MUFA) levels (-0.26 ± 0.08; P < 0.01), maternal mid upper arm circumference (MUAC) (-0.22 ± 0.11; P = 0.04), and male sex (-0.99 ± 0.45; P = 0.03) were associated with lower infant plasma n-6 PUFA levels. Infant plasma arachidonic acid (AA) levels were positively associated with maternal plasma AA levels (0.38 ± 0.09; P < 0.01), but inversely associated with twin births (-1.37 ± 0.67; P = 0.04).

CONCLUSIONS:

Greater birth weight and higher maternal plasma PUFA levels at 3 months postpartum were significantly associated with higher infant plasma PUFA levels at 3 months age. Twin births, male sex, and higher maternal MUFA levels were associated with lower infant plasma PUFA levels. Nutrition counseling for optimal intake of PUFA-rich foods, to lactating mothers in resource-limited settings may be beneficial for improved infant health.

Lipid-based nutrition supplements

Cochrane Database Syst Rev. 2019 May 2;5:CD012611. doi: 10.1002/14651858.CD012611.pub3. [Epub ahead of print] (Open access available)

Preventive lipid-based nutrient supplements given with complementary foods to infants and young children 6 to 23 months of age for health, nutrition, and developmental outcomes.

Das JK, Salam RA, Hadi YB, Sadiq Sheikh S, Bhutta AZ, Weise Prinzo Z, Bhutta ZA.

BACKGROUND:
One nutritional intervention advocated to prevent malnutrition among children is lipid-based nutrient supplements (LNS). LNS provide a range of vitamins and minerals, but unlike most other micronutrient supplements, LNS also provide energy, protein and essential fatty acids. Alternative recipes and formulations to LNS include fortified blended foods (FBF), which are foods fortified with vitamins and minerals, and micronutrient powders (MNP), which are a combination of vitamins and minerals, OBJECTIVES: To assess the effects and safety of preventive LNS given with complementary foods on health, nutrition and developmental outcomes of non-hospitalised infants and children six to 23 months of age, and whether or not they are more effective than other foods (including FBF or MNP).This review did not assess the effects of LNS as supplementary foods or therapeutic foods in the management of moderate and severe acute malnutrition.

SEARCH METHODS:
In October 2018, we searched CENTRAL, MEDLINE, Embase, 21 other databases and two trials registers for relevant studies. We also checked the reference lists of included studies and relevant reviews and contacted the authors of studies and other experts in the area for any ongoing and unpublished studies.

SELECTION CRITERIA:
Randomised controlled trials (RCTs) and quasi-RCTs that evaluated the impact of LNS plus complementary foods given at point-of-use (for any dose, frequency, duration) to non-hospitalised infants and young children aged six to 23 months in stable or emergency settings and compared to no intervention, other supplementary foods (i.e. FBF), nutrition counselling or multiple micronutrient supplements or powders for point-of-use fortification of complementary foods.

DATA COLLECTION AND ANALYSIS:

Two review authors independently screened studies for relevance and, for those studies included in the review, extracted data, assessed risk of bias and rated the quality of the evidence using the GRADE approach. We carried out statistical analysis using Review Manager software. We used a random-effects meta-analysis for combining data as the interventions differed significantly. We set out the main findings of the review in 'Summary of findings' tables.

MAIN RESULTS:
Our search identified a total of 8124 records, from which we included 17 studies (54 papers) with 23,200 children in the review. The included studies reported on one or more of the pre-specified primary outcomes, and five studies included multiple comparison groups.Overall, the majority of trials were at low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias, but at high risk of bias for blinding of participants and personnel due to the nature of the intervention. Using the GRADE approach, we judged the quality of the evidence for most outcomes as low or moderate.LNS+complementary feeding compared with no intervention Thirteen studies compared LNS plus complementary feeding with no intervention. **LNS plus complementary feeding reduced the prevalence of moderate stunting by 7% (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.88 to 0.98; nine studies, 13,372 participants; moderate-quality evidence), severe stunting by 15% (RR 0.85, 95% CI 0.74 to 0.98; five studies, 6151 participants; moderate-quality evidence), moderate wasting by 17% (RR 0.83, 95% CI 0.75 to 0.92; eight studies, 12,659 participants; moderate-quality evidence), moderate underweight by 15% (RR 0.85, 95% CI 0.80 to 0.91; eight studies, 13,073 participants; moderate-quality evidence), and anaemia by 21% (RR 0.79, 95% CI 0.69 to 0.90; five studies, 2332 participants; low-quality evidence). There was no impact of LNS plus complementary feeding on severe wasting (RR 1.27, 95% CI 0.66 to 2.46; three studies, 2329 participants) and severe underweight (RR 0.78, 95%CI 0.54 to 1.13; two studies, 1729 participants).** Adverse effects did not differ between the groups (RR 0.86, 95% CI 0.74 to 1.01; three studies, 3382 participants).LNS+complementary feeding compared with FBF Five studies compared LNS plus complementary feeding with other FBF, including corn soy blend and UNIMIX. We pooled four of the five studies in meta-analyses and found that, when compared to other FBF, LNS plus complementary feeding significantly reduced the prevalence of moderate stunting (RR 0.89, 95% CI 0.82 to 0.97; three studies, 2828 participants; moderate-quality evidence), moderate wasting (RR 0.79, 95% CI 0.65 to 0.97; two studies, 2290 participants; moderate-quality evidence), and moderate underweight (RR 0.81, 95% CI 0.73 to 0.91; two studies, 2280 participants; moderate-quality evidence). **We found no difference between LNS plus complementary feeding and FBF for severe stunting (RR 0.41, 95% CI 0.12 to 1.42; two studies, 729 participants; low-quality evidence), severe wasting (RR 0.64, 95% CI 0.19 to 2.81; two studies, 735 participants; moderate-quality evidence), and severe underweight (RR 1.23, 95% CI 0.67 to 2.25; one study, 173 participants; low-quality evidence)**. LNS+complementary feeding compared with MNP Four studies compared LNS plus complementary feeding with MNP. We pooled data from three of the four studies in meta-analyses and found that compared to MNP, LNS plus complementary feeding significantly reduced the prevalence of moderate underweight (RR 0.88, 95% CI 0.78 to 0.99; two studies, 2004 participants; moderate-quality evidence) and anaemia (RR 0.38, 95% CI 0.21 to 0.68; two studies, 557 participants; low-quality evidence). **There was no difference**

between LNS plus complementary feeding and MNP for moderate stunting (RR 0.92, 95% CI 0.82 to 1.02; three studies, 2365 participants) and moderate wasting (RR 0.97, 95% CI 0.77 to 1.23; two studies, 2004 participants).

AUTHORS' CONCLUSIONS:
The findings of this review suggest that LNS plus complementary feeding compared to no intervention is effective at improving growth outcomes and anaemia without adverse effects among children aged six to 23 months in low- and middle-income countries (LMIC) in Asia and Africa, and more effective if provided over a longer duration of time (over 12 months). Limited evidence also suggests that LNS plus complementary feeding is more effective than FBF and MNP at improving growth outcomes.

Am J Clin Nutr. 2019 Jan 1;109(1):55-68. doi: 10.1093/ajcn/nqy282. (Open access available)

Effect of small-quantity lipid-based nutrient supplements on growth, psychomotor development, iron status, and morbidity among 6- to 12-mo-old infants in South Africa: a randomized controlled trial.

Smuts CM, Matsungo TM, Malan L, Kruger HS, Rothman M, Kvalsvig JD, Covic N, Joosten K, Osendarp SJM, Bruins MJ, Frenken LGJ, Lombard CJ, Faber M.
South Africa, Switzerand, The Netherlands

Background:
Evidence on the effect of **small-quantity lipid-based nutrient supplements (SQ-LNSs)** on early child growth and development is mixed.

Objective:
This study assessed the effect of daily consumption of 2 different SQ-LNS formulations on linear growth (primary outcome), psychomotor development, iron status (secondary outcomes), and morbidity in infants from age 6 to 12 mo within the context of a maize-based complementary diet.

Methods:
Infants (n = 750) were randomly assigned to receive SQ-LNS, SQ-LNS-plus, or no supplement. Both SQ-LNS products contained micronutrients and essential fatty acids. SQ-LNS-plus contained, in addition, docosahexaenoic acid, arachidonic acid (important for brain and eye development), lysine (limiting amino acid in maize), phytase (enhances iron absorption), and other nutrients. Infants' weight and length were measured bimonthly. At age 6 and 12 mo, psychomotor development using the Kilifi Developmental Inventory and South African Parent Rating Scale and hemoglobin, plasma ferritin, C-reactive protein, and α1-acid glycoprotein were assessed. WHO Motor Milestone outcomes, adherence, and morbidity were monitored weekly through home visits. Primary analysis was by intention-to-treat, comparing each SQ-LNS group with the control.

Results:

SQ-LNS-plus had a positive effect on length-for-age z-score at age 8 mo (mean difference: 0.11; 95% CI: 0.01, 0.22; P = 0.032) and 10 mo (0.16; 95% CI: 0.04, 0.27; P = 0.008) but not at 12 mo (0.09; 95% CI: -0.02, 0.21; P = 0.115), **locomotor development score (2.05; 95% CI: 0.72, 3.38; P = 0.003)**, and Parent Rating Score (1.10; 95% CI: 0.14, 2.07; P = 0.025), but no effect for weight-for-age zscore. Both SQ-LNS (P = 0.027) and SQ-LNS-plus (P = 0.005) improved hemoglobin concentration and reduced the risk of anemia, iron deficiency, and iron-deficiency anemia. Both SQ-LNS products reduced longitudinal prevalence of fever, coughing, and wheezing but increased incidence and longitudinal prevalence of diarrhea, vomiting, and rash/sores.

Conclusions:
Point-of-use fortification with SQ-LNS-plus showed an early transient effect on linear growth and improved locomotor development. Both SQ-LNS products had positive impacts on anemia and iron status. This trial was registered at clinicaltrials.gov as NCT01845610.

Environmental enteric dysfuction

BMJ Glob Health. 2018 Dec 1;3(6):e000983. doi: 10.1136/bmjgh-2018-000983. eCollection 2018. (Open access available)

The impact of reducing dietary aflatoxin exposure on child linear growth: a cluster randomised controlled trial in Kenya.

Hoffmann V, Jones K, Leroy JL.
USA

Introduction:
Observational studies have documented an association between aflatoxin (AF) exposure and reduced linear growth in infants and young children. Our objective was to assess the effectiveness of reducing AF exposure on child linear growth and serum AF levels in rural areas in Eastern Kenya.

Methods:
A cluster randomised controlled design was used (28 intervention and 28 control clusters). The intervention arm received a swapping (contaminated maize was replaced with safe maize) and a stockist intervention (households were encouraged to purchase from a stockist supplied with clean maize). Women in the fifth to final month of pregnancy were invited to enrol in the study. Outcomes were child length-for-age Z-score (LAZ), the prevalence of stunting and child serum AFB_1-lysine adduct level 24 (endline, primary outcomes) and 11 to 19 months (midline, secondary outcomes) after trial commencement, respectively.

Results:

Of the 1230 unborn children enrolled in the study, 881 (72%) were included in the LAZ and 798 (65%) in the serum AFB_1 analysis. The intervention significantly reduced endline ln serum AFB_1-lysine adduct levels (intervention effect-0.273, 95% CI -0.547 to 0.001; one-sided p=0.025), but had no effect on endline LAZ or stunting (mean LAZ at endline was -1.64). At midline, the intervention increased LAZ by 0.16 (95% CI -0.009 to 0.33; one-sided p=0.032) and reduced stunting by seven percentage points (95% CI -0.125 to -0.007; one-sided p=0.015), but had no impact on serum AFB_1 levels.

Conclusion:
Improving access to AF-free maize substantially reduced endline serum AF, but had no effect on child linear growth. The midline analysis suggests that AF may affect linear growth at younger ages.

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

BMJ Open. 2018 Aug 5;8(8):e017573. doi: 10.1136/bmjopen-2017-017573. (Open access available)

Promoting hygienic weaning food handling practices through a community-based programme: intervention implementation and baseline characteristics for a cluster randomised controlled trial in rural Gambia.

Manjang B, Hemming K, Bradley C, Ensink J, Martin JT, Sowe J, Jarju A, Cairncross S, Manaseki-Holland S.
UK, The Gambia

OBJECTIVE:
Contamination of weaning food leads to diarrhoea in children under 5 years. Public health interventions to improve practices in low-income and middle-income countries are rare and often not evaluated using a randomised method. We describe an intervention implementation and provide baseline data for such a trial.

DESIGN:
Clustered randomised controlled trial.

SETTING:
Rural Gambia.

PARTICIPANTS:
15 villages/clusters each with 20 randomly selected mothers with children aged 6-24 months per arm.

INTERVENTION:

To develop the public health intervention, we used: (A) formative research findings to determine theoretically based critical control point corrective measures and motivational drives for behaviour change of mothers; (B) lessons from a community-based weaning food hygiene programme in Nepal and a handwashing intervention programme in India; and (C) culturally based performing arts, competitions and environmental clues. Four intensive intervention days per village involved the existing health systems and village/cultural structures that enabled per-protocol implementation and engagement of whole villager communities.

RESULTS:
Baseline village and mother's characteristics were balanced between the arms after randomisation. Most villages were farming villages accessing health centres within 10 miles, with no schools but numerous village committees and representing all Gambia's three main ethnic groups. Mothers were mainly illiterate (60%) and farmers (92%); 24% and 10% of children under 5 years were reported to have diarrhoea and respiratory symptoms, respectively, in the last 7 days (dry season). Intervention process engaged whole village members and provided lessons for future implementation; culturally adapted performing arts were an important element.

CONCLUSION:
This research has potential as a new low-cost and broadly available public health programme to reduce infection through weaning food. The theory-based intervention was widely consulted in the Gambia and with experts and was well accepted by the communities. Baseline analysis provides socioeconomic data and confirmation of Unicefs Multiple Indicator Cluster Survey (MICS) data on the prevalence of diarrhoea and respiratory symptoms in the dry season in the poorest region of Gambia.

J Nutr. 2019 Mar 1;149(3):505-512. doi: 10.1093/jn/nxy202. (Open access available)

Neither n-3 Long-Chain PUFA Supplementation of Mothers through Lactation nor of Offspring in a Complementary Food Affects Child Overall or Social-Emotional Development: A 2 × 2 Factorial Randomized Controlled Trial in Rural Ethiopia.

Argaw A, Huybregts L, Wondafrash M, Kolsteren P, Belachew T, Worku BN, Abessa TG, Bouckaert KP.
Ethiopia, Belgium, USA

BACKGROUND:
The n-3 (ω-3) long-chain polyunsaturated fatty acid (LC-PUFA) docosahexaenoic acid (DHA) is essential for optimal brain development. There is a lack of evidence on the effect of postnatal n-3 LC-PUFA supplementation on child development in low-income countries.

OBJECTIVE:

We evaluated the efficacy of fish-oil supplementation through lactation or complementary food supplementation on the development of children aged 6-24 mo in rural Ethiopia.

METHODS:
We conducted a double-blind randomized controlled trial of n-3 LC-PUFA supplementation for 12 mo using fish-oil capsules [maternal intervention: 215 mg DHA + 285 mg eicosapentaenoic acid (EPA)] or a fish-oil-enriched complementary food supplement (child intervention: 169 mg DHA + 331 mg EPA). In total, **360 pairs of mothers and infants aged 6-12 mo were randomly assigned to 4 arms: maternal intervention and child control, child intervention and maternal control, maternal and child intervention, and maternal and child control.** Primary outcomes were overall developmental performance with the use of a culturally adapted Denver II test that assesses personal-social, language, fine-motor, and gross-motor domains and social-emotional developmental performance using the Ages and Stages Questionnaire: Social Emotional at baseline and at 6 and 12 mo. We used mixed-effects models to estimate intervention effects on developmental performance over time (intervention × time interaction).

RESULTS:
The evolution in overall and social-emotional developmental performance over time did not differ across study arms (intervention × time: F = 1.09, P = 0.35, and F = 0.61, P = 0.61, respectively). Effects did not change after adjustment for child age, birth order, and nutritional status; maternal age and education; wealth; family size; and breastfeeding frequency. Children's developmental performance significantly decreased during study follow-up (β: -0.03 SDs/mo; 95% CI: -0.04, -0.01 SD/mo; P < 0.01).

CONCLUSIONS:
n-3 LC-PUFA supplementation does not affect overall or social-emotional development of children aged 6-24 mo in a low-income setting. Follow-up of the cohort is recommended to determine whether there are long-term effects of the intervention.

J Nutr. 2018 Oct 1;148(10):1605-1614. doi: 10.1093/jn/nxy147. (Open access available)

Large-Scale Social and Behavior Change Communication Interventions Have Sustained Impacts on Infant and Young Child Feeding Knowledge and Practices: Results of a 2-Year Follow-Up Study in Bangladesh.

Kim SS, Nguyen PH, Tran LM, Sanghvi T, Mahmud Z, Haque MR, Afsana K, Frongillo EA, Ruel MT, Menon P.
USA, Vietnam, Bangladesh, India

Background:
Sustained improvements in infant and young child feeding (IYCF) require continued implementation of effective interventions. From 2010-2014, Alive & Thrive (A&T) provided intensive interpersonal counseling (IPC), community mobilization (CM), and mass media (MM) in Bangladesh, demonstrating impact on IYCF practices. Since 2014, implementation has been continued and scaled up by national partners with support from other donors and

with modifications such as added focus on maternal nutrition and reduced program intensity.

Objective:
We assessed changes in intervention exposure and IYCF knowledge and practices in the intensive (IPC + CM + MM) compared with nonintensive areas (standard nutrition counseling + less intensive CM and MM) 2 y after termination of initial external donor support.

Methods:
We used a cluster-randomized design with repeated cross-sectional surveys at baseline (2010, n = 2188), endline (2014, n = 2001), and follow-up (2016, n = 2400) in the same communities, among households with children 0-23.9 mo of age. Within-group differences over time and differences between groups in changes were tested.

Results:
In intensive areas, exposure to IPC decreased slightly between endline and follow-up (88.9% to 77.2%); exposure to CM activities decreased significantly (29.3% to 3.6%); and MM exposure was mostly unchanged (28.1-69.1% across 7 TV spots). Exposure to interventions did not expand in nonintensive areas. **Most IYCF indicators in intensive areas declined from endline to follow-up, but remained higher than at baseline.** Large differential improvements of 12-17 percentage points in intensive, compared with nonintensive areas, between baseline and follow-up remained for early initiation of and exclusive breastfeeding, timely introduction of foods, and consumption of iron-rich foods. Differential impact in breastfeeding knowledge remained between baseline and follow-up; complementary feeding knowledge increased similarly in both groups.

Conclusions:
Continued IPC exposure and sustained impacts on IYCF knowledge and practices in intensive areas indicated lasting benefits from A&T's interventions as they underwent major scale-up with reduced intensity.

Curr Dev Nutr. 2019 Jun 13;3(Suppl 1). pii: nzz048.P11-112-19. doi: 10.1093/cdn/nzz048.P11-112-19. eCollection 2019 Jun.

Father Engagement in Improving Infant and Young Child Feeding (IYCF) Practices: Evidence from a Clustered Randomized Controlled Trial in Ethiopia (P11-112-19).

Han YE, Park S, Kim JE, Kim H, Hoddinott J
Author information
South Korea

Abstract
Objectives:

We identified lack of knowledge and lack of paternal support as barriers to improved IYCF practices in Ethiopia, the focus of this study. Behavior change communication (BCC) strategies are often used to improve knowledge, but BCC programs commonly target only mothers. The objective of this study is to assess the impact of both paternal and maternal BCC program on complementary feeding practices compared to maternal BCC program alone.
Methods:
This study is a community-based, clustered randomized controlled trial conducted in Ejere district, Ethiopia. We randomly selected three rural kebeles (ward) and three urban kebeles within the Ejere district. 63 garees (villages) were identified and randomly assigned within selected kebeles into treatment and control groups: T1, maternal BCC only; T2, both maternal BCC and paternal BCC; and C, control. The maternal BCC program and paternal BCC program consisted of weekly one-hour long group sessions for the duration of 16 and 12 weeks, respectively. Both BCC program included messages on improved IYCF practices. In addition, paternal BCC program included messages on gender roles.
Results:
Father's IYCF knowledge increased by 0.31SD when BCC was provided to mothers and by 0.62SD when provided to both mothers and fathers. Although we see spillover of knowledge from BCC from BCC-attending mothers to their partners in maternal BCC group, we see paternal BCC additionally increase father's knowledge by 0.36SD. The provision of both maternal and paternal BCC group improves child dietary diversity score (CDDS) by 0.64 food groups and increases the likelihood they meet minimum diet diversity by 18 percentage points. However, the additional impact of paternal BCC on child diets is not statistically significant at the 5% level. We see no differential impact on child anthropometry.
Conclusions:
Nutrition BCC program that targets both fathers and mothers have greater impact on father's knowledge, compared to nutrition BCC program that targets mothers only. However, additional knowledge gain has limited impact on IYCF practices

Comment
No Ethiopian authors included

J Hum Nutr Diet. 2019 Feb;32(1):21-30. doi: 10.1111/jhn.12595. Epub 2018 Sep 4. (Open access available)

The impact of a primary health care intervention on infant feeding practices: a cluster randomised controlled trial in Brazil.

Ferreira VR, Sangalli CN, Leffa PS, Rauber F, Vitolo MR.
Brazil

BACKGROUND:
Proper feeding practices in early life can enhance the full human potential development of children. We aimed to evaluate the impact of a primary health care intervention on infant feeding practices among children from low-income families.

METHODS:
A cluster randomised controlled trial was conducted in Porto Alegre, Brazil. Healthcare centres were randomised into intervention (n = 9) and control (n = 11) groups. In intervention sites, health workers were trained in accordance with the national guidelines. Infant feeding practices were assessed in children at 6 months (n = 617) and 12 months (n = 516) of age. Feeding practice quality was assessed using the Infant and Child Feeding Index (ICFI). Additionally, we evaluated the introduction of nonrecommended foods.

RESULTS:
At 6 months, the mean ICFI score was higher in the intervention group [MD = 0.22; 95% confidence interval (CI) = 0.24-1.11]. The prevalence of infants who met the recommendation for meat into the food-frequency score was higher in the intervention than the control group [relative risk (RR) = 1.63; 95% CI = 1.26-2.11]. **At 12 months of age, the ICFI mean (MD = 0.23; 95% CI = 0.35-0.56) and the prevalence of children who met the recommendation for dietary diversity (RR = 1.11; 95% CI = 1.01-1.22) and meal frequency (RR = 4.68; 95% CI = 1.34-16.36) were higher in the intervention group, although only among children who had more than seven follow-up appointments during the first year of life**. The children from intervention group had a significant delay for added sugar (MD = 0.51; 95% CI = 0.13-0.89), tea (mean = 0.47; 95% CI = 0.13-0.82), jelly (MD = 0.35; 95% CI = 0.11-0.58) and filled cookies (MD = 0.29; 95% CI = 0.06-0.52) compared to the control group.

CONCLUSIONS:
The health workers' training was effective with respect to improving infant feeding practices.

J Nutr. 2018 Sep 1;148(9):1484-1492. doi: 10.1093/jn/nxy136. (Open access available)

Complementary Food Supplements Increase Dietary Nutrient Adequacy and Do Not Replace Home Food Consumption in Children 6-18 Months Old in a Randomized Controlled Trial in Rural Bangladesh.

Campbell RK, Hurley KM, Shamim AA, Shaikh S, Chowdhury ZT, Mehra S, Wu L, Christian P.
USA

Background:
Inadequate complementary feeding is common in low- and middle-income countries, contributing to growth deficits. Complementary food supplements (CFSs) aim to fill dietary gaps, but few CFS studies have measured nutrient intake. In a community-based, randomized CFS trial in Bangladesh, we previously reported poor dietary diversity in 6-18-mo-old participants.

Objective:
We investigated, in a secondary analysis in the same trial, micronutrient intake adequacy in supplemented compared with control-arm children.

Methods:
At age 6 mo, children were assigned to 1 y of child-feeding counseling for mothers (control) or counseling plus 1 of 4 CFS formulations. Mothers were administered quantitative past 24-h diet questionnaires for their children at ages 6, 9, 12, 15, and 18 mo. Nutrient intakes were estimated with local recipes and food composition tables assuming average age-specific breastmilk intake. Adequacy was evaluated relative to estimated average requirements or adequate intakes. Multivariate analysis of variance and generalized estimating equation (GEE) regression models estimated the effect of each CFS on nutrient adequacy. GEE models tested dietary predictors of nutrient adequacy in the control arm.

Results:
A total of 25,964 dietary modules across 5 interviews were completed. Nutrient adequacy from home foods combined with assumed breastmilk intake was low. Only 5 of 16 micronutrients were adequately consumed by >60% of children at 18 mo of age. Daily CFSs did not affect energy-adjusted micronutrient intake from home foods at any follow-up age ($P > 0.05$). CFSs increased the mean adequacy ratio for all micronutrients ($P < 0.001$ at all ages), to ≥1 for 14 of 16 micronutrients at 18 mo. Dietary diversity predicted adequate iron, zinc and calcium intake at 15 mo in unsupplemented controls.

Conclusions:
Home foods did not meet the estimated micronutrient needs of 9-18-mo-old children in rural Bangladesh. Daily supplementation with fortified complementary foods filled many micronutrient intake gaps and did not displace home foods. Previously, CFSs were shown to also improve linear growth and reduce stunting in this cohort. Findings support the need for CFSs in similar settings to promote nutritional well being and growth.

J Nutr. 2018 Oct 1;148(10):1587-1597. doi: 10.1093/jn/nxy148. (Open access available)

Using a Community-Based Early Childhood Development Center as a Platform to Promote Production and Consumption Diversity Increases Children's Dietary Intake and Reduces Stunting in Malawi: A Cluster-Randomized Trial.

Gelli A, Margolies A, Santacroce M, Roschnik N, Twalibu A, Katundu M, Moestue H, Alderman H, Ruel M
USA, Malawi

Background:
Children in Malawi face nutritional risks related to low-quality diets and chronic malnutrition.

Objective:
This study evaluated the impact of a 1-y early childhood development (ECD) center-based agriculture and nutrition intervention aimed at improving household production diversity,

maternal knowledge on child nutrition and feeding practices, and children's diets and anthropometric measures.

Methods:
A longitudinal cluster-randomized controlled trial was implemented in 60 community-based childcare centers (CBCCs), covering 1248 preschool children (aged 36-72 mo) and 304 younger siblings (aged 6-24 mo). CBCCs were randomly assigned to 1) a control group providing the Save the Children's ECD program or 2) a treatment group providing a standard ECD program with additional activities to improve nutritious food production and behavior change communication to improve diets and care practices for young children. Primary outcomes were household production and production diversity, preschooler enrollment and attendance, and dietary intake measured by quantitative 24-h recall and minimum diet diversity for younger siblings. Secondary outcomes included anthropometric measures for preschoolers and younger siblings, child development scores for preschoolers, and women's asset ownership and time use (the latter 2 are not discussed in this article). We used difference-in-difference (DID) estimates to assess impacts.

Results:
Compared with the control group, preschool children in the intervention group had greater increases in nutrient intakes and in dietary diversity. No impacts on anthropometric measures were seen in preschoolers. Younger siblings in the intervention group had greater increases in height-for-age z scores than did children in the control group (DID: 0.44; $P < 0.05$) and greater reductions in the prevalence of stunting (DID: -17 percentage points; $P < 0.05$). The plausibility of the impact on growth in younger siblings was supported by effects along program impact pathways, including production of nutritious foods, caregiver knowledge, and dietary diversity.

Conclusion:
Implementing an integrated agriculture and nutrition intervention through an ECD platform benefited children's diets and reduced stunting among younger siblings of targeted preschoolers.

Food Nutr Bull. 2018 Sep;39(2_suppl):S35-S44. doi: 10.1177/0379572118795729. (Open access available)

Higher Levels of Dairy Result in Improved Physical Outcomes: A Synthesis of 3 Randomized Controlled Trials in Guinea-Bissau Comparing Supplements with Different Levels of Dairy Ingredients Among Children 6 to 59 Months, 5 to 19 Year Olds, and Mothers in Preschools, Primary Schools, and Villages, and the Implications for Programs.

Schlossman N.
USA

BACKGROUND:

This article synthesizes the results of 3 cluster randomized controlled trials of dairy-containing ready-to-use supplementary foods (RUSFs) to address malnutrition in primary schools, preschools and villages in Guinea-Bissau, one of the world's poorest countries. Together, these studies document widespread malnutrition across infants, young children, adolescents, and pregnant and lactating women and point to intervention options that were not previously presented.

OBJECTIVE:
To combine the evidence from the United States Department of Agriculture-funded pilot studies in Guinea-Bissau on the effects of dairy protein supplementation to gain a broader perspective on the role of dairy containing RUSFs in various age-groups, the importance of the mother-child dyad and family food dynamics for infant and child growth. Translate the results into action and the next generation of effective products.

METHODS:
A comparative analysis of data and synthesis of evidence from 3 published studies and ongoing research conducted by our team in Guinea-Bissau.

RESULTS AND CONCLUSIONS:
Higher dairy supplements have the potential to achieve broad benefits for malnutrition, especially in mothers and early childhood (first 1000 days and 36-59 months). Higher levels of dairy protein also can prevent moderate acute malnutrition in children younger than 2 years, independent of the family food dynamic. Community-level nutrition behavior change education should target older children and adolescents at the community level and through the preschool/school platform.

Comment
No authors from Guinea Bissau were included

Food Sci Nutr. 2018 Nov 20;7(1):302-311. doi: 10.1002/fsn3.890. eCollection 2019 Jan. (Open access available)

Effect of complementary foods fortified with *Moringa oleifera* leaf powder on hemoglobin concentration and growth of infants in the Eastern Region of Ghana.

Boateng L, Quarpong W, Ohemeng A, Asante M, Steiner-Asiedu M.
Ghana

Abstract
Complementary foods that are deficient in both macronutrients and micronutrients coupled with a high burden of infections during the complementary feeding period are major underlying causes of child malnutrition in developing countries. Among the recent efforts to combat malnutrition by improving the quality of complementary foods in the developing world is the use of ***Moringa oleifera*** **leaf powder (MLP) as a food fortificant. We conducted a randomized controlled trial to test the effect of feeding MLP-fortified complementary**

food on hemoglobin concentration and growth of infants and young children after 4 months of feeding. Infants aged 8-12 months were randomly assigned to receive one of three study foods; Weanimix a cereal-legume blend formulated with *Moringa* (*MCL-35g*), MLP sprinkled on infants' usual complementary foods (*MS-5g*) and the control food Weanimix without *Moringa* (*CF-35g*). Blood samples for hemoglobin determination as well as dietary intake and anthropometric data were collected at baseline and endline for 237 infants who completed the study. Data analysis was performed with SPSS (version 20) and comparisons were done by analysis of covariance (ANCOVA). There were no significant differences in hemoglobin concentration or growth indicators at endline between the three study groups. Findings of this study indicated that feeding infants a 5 g daily dose of MLP, either as part of a cereal-legume blend or as a supplement which was sprinkled on infants' usual complementary foods for 4 months, did not significantly improve infants' hemoglobin concentration or growth indicators.

Nutrients. 2019 Feb 25;11(2). pii: E480. doi: 10.3390/nu11020480. (Open access available)

Consumption of Animal-Source Protein is Associated with Improved Height-for-Age *z* Scores in Rural Malawian Children Aged 12⁻36 Months.

Kaimila Y, Divala O, Agapova SE, Stephenson KB, Thakwalakwa C, Trehan I, Manary MJ, Maleta KM.
Malawi, USA

Abstract
Linear growth faltering, caused by insufficient diet, recurrent infections and environmental enteric dysfunction (EED), continues to plague young children in low- and middle-income countries (LMICs). Diets in LMICs are primarily plant based, and thus have poor-quality protein and low levels of essential micronutrients. The aim of this study was to assess the association of the type and protein quality of food consumed with stunting, EED and acute malnutrition in children aged 6⁻36 months in Limera and Masenjere, two rural Southern Malawian communities. This is a secondary analysis of two randomized controlled trials that tested the effects of common bean and cowpea flour on stunting in children aged 6⁻36 months. We used data from two interactive 24-h dietary recalls conducted 12 weeks after enrolment into each trial. Food intakes were compared between the regions using Chi-square and Student's *t*-test. There were 355 children that participated in the dietary recalls. The diets of childrenwere of poor quality, but the children from Limera consumed more fish (54% vs. 35%, $p = 0.009$) and more bioavailable protein (26.0 ± 10.3 g/day vs. 23.1 ± 8.1 g/day, $p = 0.018$, respectively) than childrenin Masenjere. Food type and protein quality were not associated with any of the outcomes except an association between animal protein consumption and improvement in height-for-age *z* scores in childrenaged 12⁻36 months ($p = 0.047$). These findings support the notion that animal-source food (ASF) consumption in this vulnerable population promotes linear growth.

Matern Child Nutr. 2019 May 2:e12836. doi: 10.1111/mcn.12836.

Effect of locally produced complementary foods on fat-free mass, linear growth and iron status among Kenyan infants: a randomized controlled trial.

Konyole SO, Omollo SA, Kinyuru JN, Skau JKH, Owuor BO, Estambale BB, Filteau SM, Michaelsen KF, Friis H, Roos N, Owino VO.
Kenya

Abstract
The impact of quality complementary food products on infant growth and body composition has not been adequately investigated. This study evaluated the effect on fat-free mass (FFM) accrual, linear growth and iron status of locally produced complementary food products comparing to a standard product. In a randomized, double-blind trial, 499 infants at 6 mo received 9 monthly rations of: 1) WinFood Classic (WFC) comprising germinated amaranth (71%), maize (10.4%), small fish (3%) and edible termites (10%); 2) WinFood Lite (WFL) comprising germinated amaranth (82.5%), maize (10.2%) and multi-micronutrient premix; or 3) fortified Corn-soy blend plus (CSB+). Primary outcomes were changes in FFM, length, and plasma ferritin and transferrin receptors (TfR). FFM was determined using deuterium dilution. Analysis was by intention-to-treat, based on available cases. Compared to CSB+, there were no differences in change from 6 to 15 mo in FFM for WFC 0.0 kg, (95% CI:-0.30, 0.29) and WFL 0.03 kg, (95% CI:-0.25, 0.32) and length change for WFC -0.3 cm (95% CI:-0.9, 0.4) and WFL -0.3 cm (95% CI:-0.9, 0.3). TfR increased in WFC group 3.3 mg/L (95% CI: 1.7, 4.9) and WFL group 1.7 mg/L (95% CI: 0.1, 3.4) compared to CSB+. Compared to the increase in Hb in CSB+ group, there was a reduction in Hb in WFC of -0.9 g/dl (95 %CI:-1.3,-0.5) and a lower increase in WFL -0.4 g/dl (95 %CI:-0.8, 0.0). In conclusion, the tested WinFoods had the same effect on FFM and length as CSB+, while Hb and iron status decreased, suggesting inhibited iron bioavailability from the amaranth-based WinFoods.

Cochrane Database Syst Rev. 2019 Jun 17;6:CD011695. doi: 10.1002/14651858.CD011695.pub2. (Open Access available)

Nutritional interventions for preventing stunting in children (birth to 59 months) living in urban slums in low- and middle-income countries (LMIC).

Goudet SM, Bogin BA, Madise NJ, Griffiths PL.
UK

BACKGROUND:
Nutritional interventions to prevent stunting of infants and young children are most often applied in rural areas in low- and middle-income countries (LMIC). Few interventions are focused on urban slums. The literature needs a systematic assessment, as infants and children living in slums are at high risk of stunting. Urban slums are complex environments in terms of biological, social, and political variables and the outcomes of nutritional interventions need to be assessed in relation to these variables. For the purposes of this review, we followed the UN-Habitat 2004 definitions for low-income informal settlements or slums as lacking one or more indicators of basic services or infrastructure.
OBJECTIVES:

To assess the impact of nutritional interventions to reduce stunting in infants and children under five years old in urban slums from LMIC and the effect of nutritional interventions on other nutritional (wasting and underweight) and non-nutritional outcomes (socioeconomic, health and developmental) in addition to stunting.
SEARCH METHODS:
The review used a sensitive search strategy of electronic databases, bibliographies of articles, conference proceedings, websites, grey literature, and contact with experts and authors published from 1990. We searched 32 databases, in English and non-English languages (MEDLINE, CENTRAL, Web of Science, Ovid MEDLINE, etc). We performed the initial literature search from November 2015 to January 2016, and conducted top up searches in March 2017 and in August 2018.
SELECTION CRITERIA:
Research designs included randomised (including cluster-randomised) trials, quasi-randomised trials, non-randomised controlled trials, controlled before-and-after studies, pre- and postintervention, interrupted time series (ITS), and historically controlled studies among infants and children from LMIC, from birth to 59 months, living in urban slums. The interventions included were nutrition-specific or maternal education. The primary outcomes were length or height expressed in cm or length-for-age (LFA)/height-for-age (HFA) z-scores, and birth weight in grams or presence/absence of low birth weight (LBW).
DATA COLLECTION AND ANALYSIS:
We screened and then retrieved titles and abstracts as full text if potentially eligible for inclusion. Working independently, one review author screened all titles and abstracts and extracted data on the selected population, intervention, comparison, and outcome parameters and two other authors assessed half each. We calculated mean selection difference (MD) and 95% confidence intervals (CI). We performed intervention-level meta-analyses to estimate pooled measures of effect, or narrative synthesis when meta-analyses were not possible. We used P less than 0.05 to assess statistical significance and intervention outcomes were also considered for their biological/health importance. Where effect sizes were small and statistically insignificant, we concluded there was 'unclear effect'.
MAIN RESULTS:
The systematic review included 15 studies, of which 14 were randomised controlled trials (RCTs). The interventions took place in recognised slums or poor urban or periurban areas. The study locations were mainly Bangladesh, India, and Peru. The participants included 9261 infants and children and 3664 pregnant women. There were no dietary intervention studies. All the studies identified were nutrient supplementation and educational interventions. The interventions included zinc supplementation in pregnant women (three studies), micronutrient or macronutrient supplementation in children (eight studies), nutrition education for pregnant women (two studies), and nutrition systems strengthening targeting children (two studies) intervention. Six interventions were adapted to the urban context and seven targeted household, community, or 'service delivery' via systems strengthening. The primary review outcomes were available from seven studies for LFA/HFA, four for LBW, and nine for length.The studies had overall high risk of bias for 11 studies and only four RCTs had moderate risk of bias. Overall, the evidence was complex to report, with a wide range of outcome measures reported. Consequently, only eight study findings were reported in meta-analyses and seven in a narrative form. The certainty of evidence was very low to moderate overall. None of the studies reported differential impacts of interventions relevant to equity issues. Zinc supplementation of pregnant women on LBW or length (versus supplementation

without zinc or placebo) (three RCTs). There was no evidence of an effect on LBW (MD -36.13 g, 95% CI -83.61 to 11.35), with moderate-certainty evidence, or no evidence of an effect or unclear effect on length with low- to moderate-certainty evidence. Micronutrient or macronutrient supplementation in children (versus no intervention or placebo) (eight RCTs)There was no evidence of an effect or unclear effect of nutrient supplementation of children on HFA for studies in the meta-analysis with low-certainty evidence (MD -0.02, 95% CI -0.06 to 0.02), and inconclusive effect on length for studies reported in a narrative form with very low- to moderate-certainty evidence.Nutrition education for pregnant women (versus standard care or no intervention) (two RCTs)There was a positive impact on LBW of education interventions in pregnant women, with low-certainty evidence (MD 478.44g, 95% CI 423.55 to 533.32).Nutrition systems strengthening interventions targeting children (compared with no intervention, standard care) (one RCT and one controlled before-and-after study)There were inconclusive results on HFA, with very low- to low-certainty evidence, and a positive influence on length at 18 months, with low-certainty evidence.
AUTHORS' CONCLUSIONS:
All the nutritional interventions reviewed had the potential to decrease stunting, based on evidence from outside of slum contexts; however, there was no evidence of an effect of the interventions included in this review (very low- to moderate-certainty evidence). Challenges linked to urban slum programming (high mobility, lack of social services, and high loss of follow-up) should be taken into account when nutrition-specific interventions are proposed to address LBW and stunting in such environments. More evidence is needed of the effects of multi-sectorial interventions, combining nutrition-specific and sensitive methods and programmes, as well as the effects of 'up-stream' practices and policies of governmental, non-governmental organisations, and the business sector on nutrition-related outcomes such as stunting.

Breastfeeding

Matern Child Nutr. 2019 Jan 21:e12788. doi: 10.1111/mcn.12788.

Improving exclusive breastfeeding in low and middle-income countries: A systematic review.

Olufunlayo TF, Roberts AA, MacArthur C, Thomas N, Odeyemi KA, Price M, Jolly K.
Nigeria, UK

Abstract
Exclusive breastfeeding (EBF) rates until 6 months in most low and middle income countries (LMICs) are well below the 90% World Health Organization benchmark. This systematic review sought to provide evidence on effectiveness of various interventions on EBF until 6 months in LMICs, compared with standard care. Experimental and observational studies with concurrent comparator promoting EBF, conducted in LMICs with high country rates of breastfeeding initiation, were included. Studies were identified from a systematic review and PUBMED, Cochrane, and CABI databases. Study selection, data abstraction, and quality

assessment were carried out independently and in duplicate. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for individual studies and pooled. High heterogeneity was explored through prespecified subgroup analyses for the primary outcome (EBF until 6 months) by context and by intervention for the randomized controlled trials. Prediction intervals were calculated for each effect estimate. Sixty-seven studies with 79 comparisons from 30 LMICs were included. At 6 months, intervention group infants were more likely to be exclusively breastfed than controls (RR = 2.19, 95% CI [1.73, 2.77]; I 78.4%; 25 randomized controlled trials). Larger effects were obtained from interventions delivered by a combination of professional and laypersons (RR 3.90, 95% CI [1.25, 12.21]; I 46.7%), in interventions spanning antenatal and post-natal periods (RR 2.40, 95% CI [1.70, 3.38]; I 83.6%), and when intensity was between four to eight contacts/sessions (RR 3.20, 95% CI [2.30, 4.45]; I 53.8%). Almost every intervention conducted in LMICs increased EBF rates; choice of intervention should therefore be driven by feasibility of delivery in the local context to reduce infant mortality.

Lancet Glob Health. 2019 Mar;7(3):e357-e365. doi: 10.1016/S2214-109X(18)30494-7. (Open access available)

The effect of the Alive & Thrive initiative on exclusive breastfeeding in rural Burkina Faso: a repeated cross-sectional cluster randomised controlled trial.

Cresswell JA, Ganaba R, Sarrassat S, Somé H, Diallo AH, Cousens S, Filippi V.
Burkina Faso

BACKGROUND:
The benefits of exclusive breastfeeding on mortality, health, and development of children have been well documented. In Burkina Faso, the **Alive & Thrive initiative combined interpersonal communication and community mobilisation activities with the aim of improving knowledge, beliefs, skills, and, ultimately, breastfeeding outcomes**. The objective of this study was to determine **the effect of the Alive & Thrive initiative on exclusive breastfeeding in Boucle du Mouhoun, Burkina Faso**.

METHODS:
We did a cluster-randomised trial with data collected with two independent, population-representative, cross-sectional surveys: a baseline survey done before the start of the initiative implementation and an endline survey done 2 years later. Rural villages in Boucle du Mouhoun, Burkina Faso, were randomly allocated by use of computer generated pseudo-random numbers, and women were eligible for participation if they had a livebirth in the 12 months preceding the survey and resided in a village selected for the study. The primary outcome was exclusive breastfeeding among infantsyounger than 6 months. Masking was not possible for the intervention implementation. All women who participated in the trial were included in the analysis population.

FINDINGS:
Between June 2 and July 28, 2015, 2288 mothers participated in the baseline survey and between June 12 and July 25, 2017, 2253 mothers participated in the endline survey. At

endline, there was a risk difference of 38·9% (95% CI 32·2-45·6, p<0·001) between the reported prevalence of exclusive breastfeeding in the intervention group and that of the control group.

INTERPRETATION:
A multidimensional intervention deliverable at scale in a low-income setting resulted in substantial increases in mothers' optimal breastfeeding knowledge and beliefs and in reported exclusive breastfeeding practices. However, it is possible that the findings might have been influenced by social desirability bias.

Matern Child Nutr. 2018 Nov;14 Suppl 4:e12697. doi: 10.1111/mcn.12697. (Open access available)

Effectiveness of programmes and interventions to support optimal breastfeeding among children 0-23 months, South Asia: A scoping review.

Benedict RK, Craig HC, Torlesse H, Stoltzfus RJ.
USA, UNICEF, Nepal.

Abstract
Most children in South Asia are breastfed at some point in their lives; however, many are not breastfed optimally, including the early initiation of breastfeeding (EIBF) within 1 hr of birth, avoidance of prelacteal feeds (APF), exclusive breastfeeding (EBF) for 6 months, and continued breastfeeding (CBF) up to 2 years of age or beyond. This review identifies and collates evidence on the effectiveness of interventions to support optimal breastfeeding in five countries in South Asia: Afghanistan, Bangladesh, India, Nepal, and Pakistan. A scoping review was conducted of peer-reviewed and grey literature. The 31 eligible studies included randomized trials and quasi-experimental designs that were conducted between 1990 and 2015. Data were collated regarding intervention design, characteristics, and effectiveness to support EIBF, APF, EBF, and CBF. Most studies reported a positive impact on breastfeeding outcomes, including 21/25 studies that examined EIBF, 15/19 studies that examined EBF, and 10/10 studies that examined APF. The only study that examined CBF reported no effect. Education, counselling, and maternal, newborn, and child health initiatives were common intervention types with positive effects on breastfeeding outcomes. Interventions were delivered in health facility, community, and home/family environments. Programmes and interventions that reached women and their families with repeated exposure and beginning during pregnancy were more likely to improve EIBF and EBF outcomes. Interventions with no impact on breastfeeding were characterized by short duration, irregular frequency, inappropriate timing, poor coverage, and targeting.

PLoS One. 2018 Jul 16;13(7):e0200519. doi: 10.1371/journal.pone.0200519. eCollection 2018. (Open access available)

Impact of maternal nutritional supplementation in conjunction with a breastfeeding support program during the last trimester to 12 weeks

postpartum on breastfeeding practices and child development at 30 months old.

Zhang Z, Tran NT, Nguyen TS, Nguyen LT, Berde Y, Tey SL, Low YL, Huynh DTT.
Singapore, Vietnam, India.

BACKGROUND:
Maternal nutrition during pregnancy and breastfeeding is important for the healthy growth and development of the fetus and infant.

PURPOSE:
This study aimed to evaluate the long-term effects of a **maternal milk supplementation (MMS)** in conjunction with a breastfeeding support program on breastfeeding practices including duration of any breastfeeding and exclusive breastfeeding and child neurodevelopment outcomes at 30 months old.

METHODS:
We followed up the offspring of 204 Vietnamese women who completed a randomized controlled trial where the intervention group received MMS with a breastfeeding support program from the last trimester to 12 weeks postpartum while the control group received standard care. At 30 months postpartum, information on child feeding practices was collected and child neurodevelopment was assessed by the Bayley Scales of Infant and Toddler Development (Bayley-III).

RESULTS:
There was no significant difference in the duration of any breastfeeding (ABF) from birth between the groups. However, the intervention group had longer exclusive breastfeeding (EBF) duration ($p = 0.0172$), higher EBF rate at 6 months ($p = 0.0093$) and lower risk of discontinuing EBF ($p = 0.0071$) than the control. Children in the intervention group had significantly higher Bayley-III composite scores in the domains of cognitive ($p = 0.0498$) and motor ($p = 0.0422$) functions, as well as a tendency toward better social-emotional behavior ($p = 0.0513$) than children in the control group. The association between maternal intervention and child development was attenuated after further adjustment for birth weight but not EBF duration, suggesting that improvements in child development may be partially attributed to the benefits of prenatal nutrition supplementation on birth outcomes.

CONCLUSIONS:
MMS with breastfeeding support during late pregnancy and early postpartum significantly improved EBF practices. The intervention was also associated with improvements in neurodevelopment in children at 30 months old.

Comment
Trial sponsored by a milk formula company

Community nutrition and agriculture

J Nutr. 2018 Sep 1;148(9):1493-1505. doi: 10.1093/jn/nxy138. (Open access available)

PROCOMIDA, a Food-Assisted Maternal and Child Health and Nutrition Program, Reduces Child Stunting in Guatemala: A Cluster-Randomized Controlled Intervention Trial.

Olney DK, Leroy J, Bliznashka L, Ruel MT.
USA

Background:
Food-assisted maternal and child health and nutrition (FA-MCHN) programs may foster child growth during the first 1000 d (pregnancy and the first 2 y of a child's life), but evidence is scant.

Objective:
We evaluated the impact of an FA-MCHN program, PROCOMIDA, on linear growth (stunting [length-for-age z score (LAZ) < -2] and length-for-age difference [LAD]) among children aged 1-24 mo. PROCOMIDA was implemented in Guatemala by Mercy Corps and was available to beneficiaries throughout the first 1000 d.

Methods:
We used a longitudinal, cluster-randomized controlled trial with groups varying in family ration sizes [full (FFR), reduced (RFR), and none (NFR)] and individual ration types provided to mothers (pregnancy to 6 mo postpartum) and children (6-24 mo of age) [corn-soy blend (CSB), lipid-based nutrient supplement (LNS), micronutrient powder (MNP)]: 1) FFR + CSB (n = 576); 2) RFR + CSB (n = 575); 3) NFR + CSB (n = 542); 4) FFR + LNS (n = 550); 5) FFR + MNP (n = 587); 6) control (n = 574). Program impacts compared with control, and differential impacts between groups varying family ration size or individual ration type, were assessed through the use of linear mixed-effects models and post hoc simple effect tests (significant if $P < 0.05$).

Results:
PROCOMIDA significantly reduced stunting at age 1 mo in FFR + CSB, RFR + CSB, and FFR + MNP groups compared with control [5.05, 4.06, and 3.82 percentage points (pp), respectively]. Stunting impact increased by age 24 mo in FFR + CSB and FFR + MNP relative to control (impact = 11.1 and 6.5 pp at age 24 mo, respectively). For CSB recipients, the FFR compared with RFR or NFR significantly reduced stunting (6.47-9.68 pp). CSB reduced stunting significantly more than LNS at age 24 mo (8.12 pp).

Conclusions:
FA-MCHN programs can reduce stunting during the first 1000 d, even in relatively energy/food-secure populations. Large family rations with individual rations of CSB or MNP were most effective. The widening of impact as children age highlights the importance of intervening throughout the full first 1000 d. This trial was registered at clinicaltrials.gov as NCT01072279.

Comment
No authors from Guatamala incuded

Matern Child Nutr. 2018 Oct;14 Suppl 3:e12677. doi: 10.1111/mcn.12677.

An agriculture-nutrition intervention improved children's diet and growth in a randomized trial in Ghana.

Marquis GS, Colecraft EK, Kanlisi R, Aidam BA, Atuobi-Yeboah A, Pinto C, Aryeetey R.
Canada, Ghana, USA

Abstract
Stunting in Ghana is associated with rural communities, poverty, and low education; integrated agricultural interventions can address the problem. **This cluster randomized controlled trial tested the effect of a 12-month intervention (inputs and training for poultry farming and home gardening, and nutrition and health education) on child diet and nutritional status**. Sixteen clusters were identified and randomly assigned to intervention or control; communities within clusters were randomly chosen, and all interested, eligible mother-child pairs were enrolled (intervention: 8 clusters, 19 communities, and 287 households; control: 8 clusters, 20 communities, and 213 households). Intention-to-treat analyses were used to estimate the effect of the intervention on endline minimum diet diversity (≥4 food groups), consumption of eggs, and length-for-age (LAZ)/height-for-age (HAZ), weight-for-age (WAZ), and weight-for-length (WLZ)/weight-for-height (WHZ) z-scores; standard errors were corrected for clustering. Children were 10.5 ± 5.2 months (range: 0-32) at baseline and 29.8 ± 5.4 months (range: 13-48) at endline. Compared with children in the control group, children in the intervention group met minimum diet diversity (adjusted odds ratio = 1.65, 95% CI [1.02, 2.69]) and a higher LAZ/HAZ (β = 0.22, 95% CI [0.09, 0.34]) and WAZ (β = 0.15, 95% CI [0.00, 0.30]). Sensitivity analyses with random-effects and mixed-effects models and as-treated analysis were consistent with the findings. There was no group difference in WLZ/WHZ. **Integrated interventions that increase access to high-quality foods and nutrition education improve child nutrition.**

Int J Behav Nutr Phys Act. 2018 Aug 16;15(1):79. doi: 10.1186/s12966-018-0710-4. (Open access available)

The effect of the "Follow in my Green Food Steps" programme on cooking behaviours for improved iron intake: a quasi-experimental randomized community study.

Lion R, Arulogun O, Titiloye M, Shaver D, Jain A, Godwin B, Sidibe M, Adejumo M, Rosseel Y, Schmidt P.
The Netherlands, Nigeria, Belgium, Poland.

Abstract
BACKGROUND:
Nutritional iron deficiency is one of the leading factors for disease, disability and death. A quasi-experimental randomized community study in South-West Nigeria explored whether a branded behaviour change programme increased the use of green leafy vegetables (greens) and iron-fortified bouillon cubes in stews for improved iron intake.

METHODS:
A coinflip assigned the intervention to Ile-Ife (Intervention town). Osogbo (Control town) received no information. At baseline 602 mother-daughter pairs (daughters aged 12-18) were enrolled (Intervention: 300; Control: 302). A Food Frequency Questionnaire assessed the addition of cubes and greens to stews, the primary outcome. Secondary outcomes were the addition of cubes and greens to soups and changes in behavioural determinants measured using the Theory of Planned Behaviour. Structural Equation Modelling (SEM) evaluated the impact of the intervention on behavioural determinants and behaviour.

RESULTS:
The data of 527 pairs was used (Intervention: 240; Control: 287). The increase in greens added to stews was larger in the Intervention town compared to the Control town ($M_{Intervention}$ = 0.3 [SE = 0.03]; $M_{Control}$ = 0.0 [SE = 0.04], $p < 0.001$, $r = 0.36$). Change in iron-fortified cubes added to stews did not differ between towns ($p = 0.07$). The increase in cubes added to soups was larger in the Intervention town compared to the Control Town ($M_{Intervention}$ = 0.9 [SE = 0.2] vs $M_{Control}$ = 0.4 [SE = 0.1], $p < .0001$, $r = 0.20$). Unexpectedly, change in greens added to soups was larger in the Control town compared to the Intervention town ($M_{Intervention}$ = - 0.1 [SE = 0.1]; $M_{Control}$ = 0.5 [SE = 0.1], $p = 0.003$, $r = 0.15$). The intervention positively influenced awareness of anaemia and the determinants of behaviour in the Intervention town, with hardly any change in the Control town. Baseline SEMs could not be established, so no mediation analyses were done. Post-intervention SEMs highlighted the role of habit in cooking stews.

CONCLUSIONS:
The behaviour change programme increased the amount of green leafy vegetables added to stews and iron-fortified cubes added to soups. Future research should assess the long-term impact and the efficacy of the programme as it is scaled up and rolled out.

Soc Sci Med. 2019 May 16;233:93-102. doi: 10.1016/j.socscimed.2019.05.016.

Is women's empowerment a pathway to improving child nutrition outcomes in a nutrition-sensitive agriculture program?: Evidence from a randomized controlled trial in Burkina Faso.

Heckert J, Olney DK, Ruel MT
USA

Abstract
Nutrition-sensitive programs in low- and middle-income countries often aim to improve child nutrition outcomes in part by empowering women. Although previous studies have found cross-sectional associations linking women's empowerment and child nutritional status, there is limited empirical evidence supporting the hypothesis that empowering women as part of an intervention will, in turn, improve child nutritional outcomes. We tested this hypothesis using two waves of data from a cluster-randomized controlled trial of a nutrition-sensitive agricultural program in Burkina Faso. With structural equation models, we examined whether **four domains of women's empowerment-purchasing decisions, healthcare decisions, family planning decisions, and spousal communication**-mediated the program's impact on reducing wasting and increasing hemoglobin among children who

were three to 12 months old at the start of the two-year program. **We found that improvements in women's empowerment in the domains of spousal communication, purchasing decisions, healthcare decisions, and family planning decisions contributed to the program's impact on reducing wasting with the largest share being attributable to spousal communication**. Improvements in women's empowerment did not contribute to the increase in hemoglobin. These findings provide the first evidence from a randomized controlled trial that women's empowerment is a pathway by which a nutrition-sensitive program can improve child wasting. **Programs that aim to improve child nutritional status should incorporate interventions designed to empower women**.

Comment
No authors from Burkina Faso included

Obesity

Int J Environ Res Public Health. 2019 Jan 15;16(2). pii: E232. doi: 10.3390/ijerph16020232. (Open access available)

Effect of a Multidimensional Physical Activity Intervention on Body Mass Index, Skinfolds and Fitness in South African Children: Results from a Cluster-Randomised Controlled Trial.

Müller I, Schindler C, Adams L, Endes K, Gall S, Gerber M, Htun NSN, Nqweniso S, Joubert N, Probst-Hensch N, du Randt R, Seelig H, Smith D, Steinmann P, Utzinger J, Yap P, Walter C, Pühse U.
Switzerland, South Africa, Singapore, South Africa

Abstract
Obesity-related conditions impose a considerable and growing burden on low- and middle-income countries, including South Africa. **We aimed to assess the effect of twice a 10-week multidimensional, school-based physical activity intervention on children's health in Port Elizabeth, South Africa**. A cluster-randomised controlled trial was implemented from February 2015 to May 2016 in grade 4 classes in eight disadvantaged primary schools. **Interventions consisted of physical education lessons, moving-to-music classes, in-class activity breaks and school infrastructure enhancement to promote physical activity. Primary outcomes included cardiorespiratory fitness, body mass index (BMI) and skinfold thickness.** Explanatory variables were socioeconomic status, self-reported physical activity, stunting, anaemia and parasite infections. Complete data were available from 746 children. **A significantly lower increase in the mean BMI Z-score (estimate of difference in mean change: -0.17; 95% confidence interval (CI): -0.24 to -0.09; $p < 0.001$) and reduced increase in the mean skinfold thickness (difference in mean change: -1.06; 95% CI: -1.83 to -0.29; $p = 0.007$) was observed in intervention schools.** No significant group difference occurred in the mean change of cardiorespiratory fitness ($p > 0.05$). These findings show that a multidimensional, school-based physical activity intervention can reduce the

increase in specific cardiovascular risk factors. However, a longer and more intensive intervention might be necessary to improve cardiorespiratory fitness.

Oncology

(see also HIV – management of HIV related conditions)

Cochrane Database Syst Rev. 2019 Mar 19;3:CD009031. doi: 10.1002/14651858.CD009031.pub2. (Open access available)

Outpatient treatment for people with cancer who develop a low-risk febrile neutropaenic event.

Rivas-Ruiz R, Villasis-Keever M, Miranda-Novales G, Castelán-Martínez OD, Rivas-Contreras S. Brazil

BACKGROUND:
People with febrile neutropaenia are usually treated in a hospital setting. Recently, treatment with oral antibiotics has been proven to be as effective as intravenous therapy. However, the efficacy and safety of outpatient treatment have not been fully evaluated.

OBJECTIVES:
To compare the efficacy (treatment failure and mortality) and safety (adverse events of antimicrobials) of outpatient treatment compared with inpatient treatment in people with cancer who have low-risk febrile neutropaenia.

SEARCH METHODS:
We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 11) in the Cochrane Library, MEDLINE via Ovid (from 1948 to November week 4, 2018), Embase via Ovid (from 1980 to 2018, week 48) and trial registries (National Cancer Institute, MetaRegister of Controlled Trials, Medical Research Council Clinical Trial Directory). We handsearched all references of included studies and major reviews.

SELECTION CRITERIA:
Randomised controlled trials (RCTs) comparing outpatient with inpatient treatment for people with cancer who develop febrile neutropaenia. The outpatient group included those who started treatment as an inpatient and completed the antibiotic course at home (sequential) as well as those who started treatment at home.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed trial eligibility, methodological quality, and extracted data. Primary outcome measures were: treatment failure and mortality; secondary outcome measures considered were: duration of fever, adverse drug reactions to antimicrobial treatment, duration of neutropaenia, duration of hospitalisation, duration of antimicrobial treatment, and quality of life (QoL). We estimated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data; we calculated weighted mean differences

for continuous data. Random-effects meta-analyses and sensitivity analyses were conducted.

MAIN RESULTS:
We included ten RCTs, six in adults (628 participants) and four in children (366 participants). We found no clear evidence of a difference in treatment failure between the outpatient and inpatient groups, either in adults (RR 1.23, 95% CI 0.82 to 1.85, I 0%; six studies; moderate-certainty evidence) or children (RR 1.04, 95% CI 0.55 to 1.99, I 0%; four studies; moderate-certainty evidence). For mortality, we also found no clear evidence of a difference either in studies in adults (RR 1.04, 95% CI 0.29 to 3.71; six studies; 628 participants; moderate-certainty evidence) or in children (RR 0.63, 95% CI 0.15 to 2.70; three studies; 329 participants; moderate-certainty evidence). According to the type of intervention (early discharge or exclusively outpatient), meta-analysis of treatment failure in four RCTs in adults with early discharge (RR 1.48, 95% CI 0.74 to 2.95; P = 0.26, I 0%; 364 participants; moderate-certainty evidence) was similar to the results of the exclusively outpatient meta-analysis (RR 1.15, 95% CI 0.62 to 2.13; P = 0.65, I 19%; two studies; 264 participants; moderate-certainty evidence). Regarding the secondary outcome measures, we found no clear evidence of a difference between outpatient and inpatient groups in duration of fever (adults: mean difference (MD) 0.2, 95% CI -0.36 to 0.76, 1 study, 169 participants; low-certainty evidence) (children: MD -0.6, 95% CI -0.84 to 0.71, 3 studies, 305 participants; low-certainty evidence) and in duration of neutropaenia (adults: MD 0.1, 95% CI -0.59 to 0.79, 1 study, 169 participants; low-certainty evidence) (children: MD -0.65, 95% CI -0.1.86 to 0.55, 2 studies, 268 participants; moderate-certainty evidence). With regard to adverse drug reactions, although there was greater frequency in the outpatient group, we found no clear evidence of a difference when compared to the inpatient group, either in adult participants (RR 8.39, 95% CI 0.38 to 187.15; three studies; 375 participants; low-certainty evidence) or children (RR 1.90, 95% CI 0.61 to 5.98; two studies; 156 participants; low-certainty evidence). Four studies compared the hospitalisation time and found that the mean number of days of hospital stay was lower in the outpatient treated group by 1.64 days in adults (MD -1.64, 95% CI -2.22 to -1.06; 3 studies, 251 participants; low-certainty evidence) and by 3.9 days in children (MD -3.90, 95% CI -5.37 to -2.43; 1 study, 119 participants; low-certainty evidence). In the 3 RCTs of children in which days of antimicrobial treatment were analysed, we found no difference between outpatient and inpatient groups (MD -0.07, 95% CI -1.26 to 1.12; 305 participants; low-certainty evidence).We identified two studies that measured QoL: one in adults and one in children. QoL was slightly better in the outpatient group than in the inpatient group in both studies, but there was no consistency in the domains included.

AUTHORS' CONCLUSIONS:
Outpatient treatment for low-risk febrile neutropaenia in people with cancer probably makes little or no difference to treatment failure and mortality compared with the standard hospital (inpatient) treatment and may reduce time that patients need to be treated in hospital.

J Pediatr Hematol Oncol. 2019 May;41(4):294-297. doi: 10.1097/MPH.0000000000001357.

Palonosetron is a Better Choice Compared With Ondansetron for the Prevention of Chemotherapy-induced Nausea and Vomiting (CINV) in a Resource-limited Pediatric Oncology Center: Results From a Randomized Control Trial.

Chaudhary NK, John RR, Boddu D, Mahasampath G, Nesadeepam N, Mathew LG.
India

Abstract
Palonosetron (PG) is a newer, safe, and effective long-acting 5-HT3 antagonist commonly used in adults, but data in children are limited. **A randomized controlled trial was carried out among children with cancer during their first cycle of moderate or highly emetogenic chemotherapy to receive either PG or ondansetron (OG) with the aim of comparing their efficacy, safety, and cost-effectiveness.** In total, 200 children (mean age, 8 y, male:female=1.8:1) were recruited, 100 in each arm. **Complete response, defined as no vomiting, in acute (<24 h), delayed (24 to 120 h), and overall phases (0 to 120 h) was observed in 88%, 88%, and 81% of cases, respectively, for PG versus 84%, 79%, and 72%, respectively, for OG (P=0.42, 0.09 and 0.21, respectively)**. Complete protection rates, defined as no nausea and vomiting in children above 6 years of age, in acute, delayed, and overall phases were 84%, 81%, and 73%, respectively, for PG versus 79%, 67%, and 60%, respectively, for OG (P=0.44, 0.06 and 0.10, respectively). **Overall, the efficacy and safety of PG in the prevention of chemotherapy-induced nausea and vomiting was comparable with OG, but PG was a more cost-effective and suitable choice for busy centers in resource-limited countries.**

Pediatr Blood Cancer. 2019 Mar;66(3):e27551. doi: 10.1002/pbc.27551. Epub 2018 Nov 13.
(Open access available)

Intravenous fosaprepitant for the prevention of chemotherapy-induced vomiting in children: A double-blind, placebo-controlled, phase III randomized trial.

Radhakrishnan V, Joshi A, Ramamoorthy J, Rajaraman S, Ganesan P, Ganesan TS, Dhanushkodi M, Sagar TG.
India

Abstract
BACKGROUND:
Fosaprepitant is a neurokinin-1 receptor antagonist, approved for the prevention of chemotherapy-induced nausea and vomiting. The data on the use of fosaprepitant in children are limited and therefore we conducted a phase III randomized controlled trial.

PROCEDURE:
Children aged 1-12 years scheduled to receive moderately or highly emetogenic chemotherapy were randomly assigned to arm-A (fosaprepitant) or arm-B (placebo).

Children recruited to arm-A received intravenous ondansetron plus dexamethasone followed by fosaprepitant infusion. Children recruited to arm-B received the same drugs as those given to children in arm-A, except that fosaprepitant was substituted with a placebo. Ondansetron and dexamethasone were continued for 48 hours after completion of chemotherapy. The primary end point of the study was to determine the proportion of patients who achieved a complete response (CR), defined as no vomiting, no retching, and no use of rescue medication, during the 24-120 hours (delayed phase) after administration of the last dose of chemotherapy. Secondary end points were the proportion of patients who achieved a CR during the acute phase (0-24 hours) and overall after administration of the last dose of chemotherapy.

RESULTS:
One-hundred-sixty-three patients were analyzed (81 in the fosaprepitant arm and 82 in the placebo arm). CR rates were significantly higher in the fosaprepitant arm compared to those in the placebo arm during the acute phase (86% vs 60%, P < 0.001), delayed phase (79% vs 51%, P < 0.001), and overall phase (70% vs 41%, P < 0.001). Three (4%) patients in the fosaprepitant arm and sixteen (20%) in the placebo arm required rescue anti-emetics (P = 0.0017).

CONCLUSION:
Addition of fosaprepitant to ondansetron and dexamethasone improved chemotherapy-induced vomiting control in children treated with moderately or highly emetogenic chemotherapy.

Complement Ther Med. 2018 Dec;41:180-185. doi: 10.1016/j.ctim.2018.09.020. Epub 2018 Sep 28.

Effectiveness of group art therapy on quality of life in paediatric patients with cancer: A randomized controlled trial.

Abdulah DM, Abdulla BMO.
Iraq

OBJECTIVES:
Children with cancer undergoing chemotherapy experience many adverse effects. The effectiveness of painting- and handcrafting-based art therapy on the various dimensions of health-related quality of life in paediatric outpatients previously diagnosed with heterogeneity of malignancy was evaluated in the present study.

DESIGN:
In an experimental randomized controlled trial, a total of 60 children aged 7-13 years previously diagnosed with malignancy together with their parents were assigned randomly either to an experimental (30 patients) or a control group (30 patients) in 2017 in Iraq. **The patients in the experimental group participated in painting and handcrafting group art therapy (creative art therapy) conducted by a professional fine artist for a one-month**

period. The dimensions of health-related quality of life in both study groups were measured through the KIDSCREEN-10 Index after project completion.

RESULTS:
The patients in the experimental group were significantly more physically active and energetic (P < 0.001), were less depressed and emotional, and had fewer stressful feelings (P = 0.004). Moreover, they enjoyed their social and leisure time more and participated more in social activities (P = 0.003) in addition to an improvement in their relationships with other children (P = 0.043) and had better overall health status (P < 0.001). However, the children's overall interaction with other children, parents, and healthcare providers (P = 0.074) and their perception of cognitive capacity for school performance (P = 0.257) were not significantly different between the two groups.

CONCLUSIONS:
The findings of the study suggest that exposure to painting- and handcrafting-based art therapy improves the overall health-related quality of life in children with cancer.

Ophthalmology and optometry

Int J Environ Res Public Health. 2018 Dec 8;15(12). pii: E2783. doi: 10.3390/ijerph15122783. (Open access available)

Impact of a Local Vision Care Center on Glasses Ownership and Wearing Behavior in Northwestern Rural China: A Cluster-Randomized Controlled Trial.

Ma Y, Gao Y, Wang Y, Li H, Ma L, Jing J, Shi Y, Guan H, Congdon N.
China, USA, UK, USA

Abstract
Visual impairment is common among rural Chinese children, but fewer than a quarter of children who need glasses actually own and use them. To study the effect of rural county hospital vision centers (VC) on self-reported glasses ownership and wearing behavior (primary outcome) among rural children in China, we conducted a cluster-randomized controlled trial at a VC in the government hospital of Qinan County, a nationally-designated poor county. All rural primary schools (*n* = 164) in the county were invited to participate. **Schools were randomly assigned to either the treatment group to receive free vision care and eyeglasses, if needed, or control group, who received glasses only at the end of the study.** Among 2806 eligible children with visiual impairment (visual acuity ≤ 6/12 in either eye), 93 (3.31%) were lost to follow-up, leaving 2713 students (45.0% boys). Among these, glasses ownership at the end of the school year was 68.6% among 1252 treatment group students (82 schools), and 26.4% ($p < 0.01$) among 1461 controls (82 schools). The rate of wearing glasses was 55.2% in the treatment group and 23.4% ($p < 0.01$) among the control group. In logistic regression models, treatment group membership was significantly associated with spectacle ownership (Odds Ratio [OR] = 11.9, $p < 0.001$) and wearing

behavior (OR = 7.2, $p < 0.001$). County hospital-based vision centers appear effective in delivering childrens' glasses in rural China.

Int J Environ Res Public Health. 2018 Dec 5;15(12). pii: E2749. doi: 10.3390/ijerph15122749.

The Effect of Providing Free Eyeglasses on Children's Mental Health Outcomes in China: A Cluster-Randomized Controlled Trial.

Guan H, Wang H, Du K, Zhao J, Boswell M, Shi Y, Qian Y.
China, USA

Abstract
If children with common vision problems receive and use eyeglasses, their educational performance rises. Without proper treatment, visually impaired children may not achieve educational gains and could suffer from poor mental health. **We use a randomized controlled trial to study the impact of an eyeglasses promotion program in rural China on the mental health of myopic primary school students.** Three measures of mental health are used: learning anxiety, physical anxiety, and scores on the Mental Health Test (MHT). Our empirical analysis showed that on average, the treatment has small and insignificant for learning anxiety and MHT, and a small but significant reduction in physical anxiety. However, subgroup analysis reveals that myopic students who study more intensively see their learning anxiety and physical anxiety reduced after being provided with eyeglasses. In contrast, students with the lower study intensity suffer a rise in learning anxiety after receiving eyeglasses. A potential mechanism for the differing impacts is the increase in teasing reported among low study-intensity students that does not occur for high study-intensity students. Care should be taken to maximize the benefits and minimize the costs of in-school vision programs.

Lancet Glob Health. 2018 Aug;6(8):e924-e932. doi: 10.1016/S2214-109X(18)30244-4.

Smartphone-based screening for visual impairment in Kenyan school children: a cluster randomised controlled trial.

Rono HK, Bastawrous A, Macleod D, Wanjala E, Di Tanna GL, Weiss HA, Burton MJ.
Kenya, UK

BACKGROUND:
Childhood visual impairment is a major public health concern that requires effective screening and early intervention. We investigated the effectiveness of Peek school eye health, a smartphone-based sight test and referral system (comprising Peek Acuity test, sight simulation referral cards, and short message service [SMS] reminders), versus standard care (Snellen's Tumbling-E card and written referral).

METHODS:
We initially compared the performance of both the Snellen Tumbling-E card and the Peek Acuity test to a standard backlit EDTRS LogMAR visual acuity test chart. We did a cluster

randomised controlled trial to **compare the Peek school eye health system with standard school screening care, delivered by school teachers**. Schools in Trans Nzoia County, Kenya, were eligible if they did not have an active screening programme already in place. Schools were randomly allocated (1:1) to either the Peek school eye health screening and referral programmes (Peek group) or the standard care screening and referral programme (standard group). In both groups, teachers tested vision of children in years 1-8. Pupils with visual impairment (defined as vision less than 6/12 in either eye) were referred to hospital for treatment. Referred children from the standard group received a written hospital referral letter. **Participants and their teachers in the Peek group were shown their simulated sight on a smartphone and given a printout of this simulation with the same hospital details as the standard referral letter to present to their parent or guardian.** They also received regular SMS reminders to attend the hospital. The primary outcome was the proportion of referred children who reported to hospital within 8 weeks of referral. Primary analysis was by intention to treat, with the intervention effect estimated using odds ratios. This trial is registered with Pan African Clinical Trial Registry, number PACTR201503001049236.

FINDINGS:
Sensitivity was similar for the Peek test and the standard test (77% [95% CI 64·8-86·5] vs 75% [63·1-85·2]). Specificity was lower for the Peek test than the standard test (91% [95% CI 89·3-92·1] vs 97·4% [96·6-98·1]). Trial recruitment occurred between March 2, 2015, and March 13, 2015. Of the 295 eligible public primary schools in Trans Nzoia County, 50 schools were randomly selected and assigned to either the Peek group (n=25) or the standard group (n=25). 10 579 children were assessed for visual impairment in the Peek group and 10 284 children in the standard group. Visual impairment was identified in 531 (5%) of 10 579 children in the Peek group and 366 (4%) of 10 284 children in the standard care group. The proportion of pupils identified as having visual impairment who attended their hospital referral was significantly higher in the Peek group (285 [54%] of 531) than in the standard group (82 [22%] of 366; odds ratio 7·35 [95% CI 3·49-15·47]; p<0·0001).

INTERPRETATION:
The Peek school eye health system increased adherence to hospital referral for visual impairment assessment compared with the standard approach among school children. This indicates the potential of this technology package to improve uptake of services and provide real-time visibility of health service delivery to help target resources.

Optom Vis Sci. 2018 Sep;95(9):873-882. doi: 10.1097/OPX.0000000000001270. (Open access available)

Randomized Trial of Tablet Computers for Education and Learning in Children and Young People with Low Vision.

Gothwal VK, Thomas R, Crossland M, Bharani S, Sharma S, Unwin H, Xing W, Khabra K, Dahlmann-Noor A.
India, UK

SIGNIFICANCE:
Mobile devices such as tablet computers have become widely available as mainstream devices and are also used in some schools, but there is an absence of robust information regarding the efficacy of any optical/electronic low vision device or tablet computer in supporting education of young people with low vision.

PURPOSE:
A randomized controlled trial (RCT) is needed to measure the impact of tablet computers on education, specifically on independent access to educational material, in children and young people with low vision. We conducted a pilot RCT to determine the feasibility of conducting a full-scale trial.

METHODS:
This was a randomized multicenter pilot trial across two sites in the United Kingdom and one site in India. Forty children and young people aged 10 to 18 years with low vision (best-corrected visual acuity for distance between <20/60 [0.48 logMAR] and 20/400 [1.30 logMAR] in the better eye) in the United Kingdom (n = 20) and India (n = 20) were randomized to two parallel arms, with a 1:1 allocation ratio, to control (n = 20) or intervention (n = 20). Control group participants received standard low vision care. The intervention group received a tablet computer (iPad) with low vision applications and instruction in its use, including accessibility features. Four primary outcomes included (1) 6-month recruitment rate, (2) retention of participants for 3 months, (3) acceptance/usage of device, and (4) accessibility of device.

RESULTS:
Nineteen participants (95%) enrolled within 6 months in the United Kingdom, and 20 participants (100%), in India. Retention at 3 months was 85% (n = 17) in the United Kingdom and 95% (n = 19) in India. More than one half of participants reported using a tablet computer at school at least once every day. The majority (90%) found it easily accessible.

CONCLUSIONS:
This study demonstrated that it is feasible to recruit children and young people with low vision into an international multicenter RCT of electronic assistive technology. **Regardless of geographical location, children and young people with low vision reported using tablet computers at least once a day at school and accessed them easily.**

Trachoma

Ophthalmic Epidemiol. 2019 Feb;26(1):19-26. doi: 10.1080/09286586.2018.1512635. Epub 2018 Aug 28. (Open access available)

A Longitudinal Analysis of Chlamydial Infection and Trachomatous Inflammation Following Mass Azithromycin Distribution.

Morberg DP, Alemayehu W, Melese M, Lakew T, Sisay A, Zhou Z, Cevallos V, Oldenburg CE, Porco TC, Lietman TM, Keenan JD.
USA, Ethiopia

BACKGROUND:
Mass azithromycin distributions are effective for clearing ocular strains of Chlamydia trachomatis, yet infection frequently returns in areas with hyperendemic trachoma. A better understanding of the factors associated with chlamydial reinfection could be helpful to plan trachoma elimination strategies.

METHODS:
This was a prospective cohort study conducted in a trachoma-hyperendemic region of Ethiopia in 2003. As part of a larger cluster-randomized trial, 21 villages were treated with a single mass azithromycin distribution and all children 5 years and younger were monitored for ocular chlamydia and clinically active trachoma at baseline and at 2 and 6 months following the treatment.

RESULTS:
In 20 villages with available data, azithromycin treatment coverage was 88.7% (95% confidence interval [CI] 85.7-91.8%). In total, 1005 children tested negative for ocular chlamydia at the 2-month visit, of whom 41 became infected by 6 months (1.0 incident chlamydia infections per 100 person-months, 95%CI 0.7-1.4). The presence of intense trachomatous inflammation (TI) at baseline was associated with incident infection at 6 months (incidence rate ratio 1.91, 95%CI 1.03-3.55). Ocular chlamydia infections clustered more within households than communities: (intraclass correlation coefficient 0.01 for communities and 0.29 for households six months posttreatment). Younger children were more likely to have persistent clinically active trachoma (P = 0.03).

CONCLUSIONS:
More intensive antibiotic distributions may be warranted for younger children, for children with TI, and for households containing children with ocular chlamydia infections.

PLoS Med. 2018 Aug 14;15(8):e1002633. doi: 10.1371/journal.pmed.1002633. eCollection 2018 Aug. (Open access available)

Mass azithromycin distribution for hyperendemic trachoma following a cluster-randomized trial: A continuation study of randomly reassigned subclusters (TANA II).

Keenan JD, Tadesse Z, Gebresillasie S, Shiferaw A, Zerihun M, Emerson PM, Callahan K, Cotter SY, Stoller NE, Porco TC, Oldenburg CE, Lietman TM.
USA, Ethiopia

BACKGROUND:
The World Health Organization recommends annual mass azithromycin administration in communities with at least 10% prevalence of trachomatous inflammation-follicular (TF) in

children, with further treatment depending on reassessment after 3-5 years. However, **the effect of stopping mass azithromycin distribution after multiple rounds of treatment is not well understood.** Here, we report the **results of a cluster-randomized trial where communities that had received 4 years of treatments were then randomized to continuation or discontinuation of treatment.**

METHODS AND FINDINGS:
In all, 48 communities with 3,938 children aged 0-9 years at baseline in northern Ethiopia had received 4 years of annual or twice yearly mass azithromycin distribution as part of the TANA I trial. We randomized these communities to either continuation or discontinuation of treatment. Individuals in the communities in the continuation arm were offered either annual or twice yearly distribution of a single directly observed dose of oral azithromycin. The primary outcome was community prevalence of ocular chlamydial infection in a random sample of children aged 0-9 years, 36 months after baseline. We also assessed the change from baseline to 36 months in ocular chlamydia prevalence within each arm. We compared 36-month ocular chlamydia prevalence in communities randomized to continuation versus discontinuation in a model adjusting for baseline ocular chlamydia prevalence. A secondary prespecified analysis assessed the rate of change over time in ocular chlamydia prevalence between arms. In the continuation arm, mean antibiotic coverage was greater than 90% at all time points. In the discontinuation arm, the mean prevalence of infection in children aged 0-9 years increased from 8.3% (95% CI 4.2% to 12.4%) at 0 months to 14.7% (95% CI 8.7% to 20.8%, P = 0.04) at 36 months. Ocular chlamydia prevalence in communities where mass azithromycin distribution was continued was 7.2% (95% CI 3.3% to 11.0%) at baseline and 6.6% (95% CI 1.1% to 12.0%, P = 0.64) at 36 months. The 36-month prevalence of ocular chlamydia was significantly lower in communities continuing treatment compared with those discontinuing treatment (P = 0.03). Limitations of the study include uncertain generalizability outside of trachoma hyperendemic regions.

CONCLUSIONS:
In this study, ocular chlamydia infection rebounded after 4 years of periodic mass azithromycin distribution. Continued distributions did not completely eliminate infection in all communities or meet WHO control goals, although they did prevent resurgence.

Ophthalmic Epidemiol. 2019 Feb;26(1):1-6. doi: 10.1080/09286586.2017.1293693. Epub 2018 Dec 13. (Open access available)

Evaluation of a Single Dose of Azithromycin for Trachoma in Low-Prevalence Communities.

Wilson N, Goodhew B, Mkocha H, Joseph K, Bandea C, Black C, Igietseme J, Munoz B, West SK, Lammie P, Kasubi M, Martin DL.
USA, Tanzania

PURPOSE:

Trachoma, caused by repeated ocular infection with Chlamydia trachomatis, is the leading infectious cause of blindness worldwide and is targeted for elimination as a public health problem. **We sought to determine whether a one-time azithromycin mass treatment would reduce trachomatous inflammation-follicular (TF) levels below the elimination threshold of 5% in communities with disease prevalence between 5 and 9.9%.**

METHODS:
The study was conducted in 96 sub-village units (balozis) in the Kongwa district of Tanzania which were predicted from prior prevalence surveys to have TF between 5 and 9.9%. Balozis were randomly assigned to the intervention and control arms. The intervention arm received a single mass drug administration of azithromycin. At baseline and 12-month follow-up, ocular exams for trachoma, ocular swabs for detection of chlamydial DNA, and finger prick blood for analysis of anti-chlamydial antibody were taken.

RESULTS:
Comparison of baseline and 12-month follow-up showed no significant difference in the overall TF_{1-9} prevalence by balozi between control and treatment arms. **In the treatment arm there was a significant reduction of ocular infection 12 months after treatment (p = 0.004) but no change in the control arm.** No change in Pgp3-specific antibody responses were observed after treatment in the control or treatment arms. Anti-CT694 responses increased in both study arms (p = 0.009 for control arm and p = 0.04 for treatment arm).

CONCLUSION:
These data suggest that a single round of MDA may not be sufficient to decrease TF levels below 5% when TF_{1-9} is between 5 and 9.9% at baseline.

PLoS Negl Trop Dis. 2019 Jan 28;13(1):e0007127. doi: 10.1371/journal.pntd.0007127. eCollection 2019 Jan. (Open access available)

Community-level chlamydial serology for assessing trachoma elimination in trachoma-endemic Niger.

Kim JS, Oldenburg CE, Cooley G, Amza A, Kadri B, Nassirou B, Cotter SY, Stoller NE, West SK, Bailey RL, Keenan JD, Gaynor BD, Porco TC, Lietman TM, Martin DL.
USA, Niger

BACKGROUND:
Program decision-making for trachoma elimination currently relies on conjunctival clinical signs. Antibody tests may provide additional information on the epidemiology of trachoma, particularly in regions where it is disappearing or elimination targets have been met.

METHODS:
A cluster-randomized trial of mass azithromycin distribution strategies for trachoma elimination was conducted over three years in a mesoendemic region of Niger. **Dried blood spots were collected from a random sample of children aged 1-5 years in each of 24**

study communities at 36 months after initiation of the intervention. A multiplex bead assay was used to test for antibodies to two Chlamydia trachomatis antigens, Pgp3 and CT694. We compared seropositivity to either antigen to clinical signs of active trachoma (trachomatous inflammation-follicular [TF] and trachomatous inflammation-intense [TI]) at the individual and cluster level, and to ocular chlamydia prevalence at the community level.

RESULTS:
Of 988 children with antibody data, TF prevalence was 7.8% (95% CI 6.1 to 9.5) and TI prevalence was 1.6% (95% CI 0.9 to 2.6). The overall prevalence of antibody positivity to Pgp3 was 27.2% (95% CI 24.5 to 30), and to CT694 was 23.7% (95% CI 21 to 26.2). Ocular chlamydia infection prevalence was 5.2% (95% CI 2.8 to 7.6). Seropositivity to Pgp3 and/or CT694 was significantly associated with TF at the individual and community level and with ocular chlamydia infection and TI at the community level. Older children were more likely to be seropositive than younger children.

CONCLUSION:
Seropositivity to Pgp3 and CT694 correlates with clinical signs and ocular chlamydia infection in a mesoendemic region of Niger.

Oral health / dentistry

Spec Care Dentist. 2019 Mar;39(2):125-134. doi: 10.1111/scd.12350. Epub 2018 Dec 30.

Effectiveness of a novel oral health education technique in maintenance of gingival health and plaque removal efficacy among institutionalized visually impaired children of Bhubaneswar city: A randomized controlled trial.

Das D, Suresan V, Jnaneswar A, Pathi J, Bala Subramaniam G.
India

AIM:
This study aimed to assess the effectiveness of a novel health education method-Audio Tactile Performance (ATP) technique-in maintenance of gingival health and plaque removal efficacy among institutionalized visually impaired children of Bhubaneswar city.

METHODS AND RESULTS:
A parallel arm, single blinded randomized controlled trial was conducted among 10- to 15-year-old visually impaired children. Clinical examinations were done by the examiner blinded to group allocations. Oral health education materials (Braille and audio) were given to control group and ATP technique was given to test group. Clinical examinations for plaque and gingival scores were assessed at baseline, 30 days interval, and 90 days interval. In control group, a greater plaque reduction was observed at 30 days interval (3.58 ± 1.3) when

compared to baseline (2.63 ± 2.02) and 90 days interval (3.14 ± 0.88), and this difference was statistically significant. For whole mouth, in test group, a greater reduction in gingival scores was observed at 90 days interval (2.65 ± 1.64) when compared to baseline (4.58 ± 1.63) and 30 days interval (1.23 ± 2.43), and this difference was statistically significant.

CONCLUSION:
ATP was found to be at par with the control group (Braille and audio aids).

Int J Clin Pediatr Dent. 2018 Mar-Apr;11(2):66-70. doi: 10.5005/jp-journals-10005-1487. Epub 2018 Apr 1.

Comparison of the Effectiveness of Probiotic, Chlorhexidine-based Mouthwashes, and Oil Pulling Therapy on Plaque Accumulation and Gingival Inflammation in 10- to 12-year-old Schoolchildren: A Randomized Controlled Trial.

Kandaswamy SK, Sharath A, Priya PG.
India

Introduction:
The use of a mouthwash augments mechanical removal of plaque by brushing and flossing and helps maintain oral health through its antiplaque and antibacterial chemical properties.

Aim:
To evaluate the effectiveness of a probiotic mouthwash, sesame oil pulling therapy, and chlorhexidine-based mouth-wash on plaque accumulation and gingival inflammation in schoolchildren aged 10 to 12 years.

Materials and methods:
The randomized controlled trial included 45 healthy schoolchildren aged 10 to 12 years and studying in Government High School, Tiruchengode, Tamil Nadu, India. The participants were randomly divided into three groups, I, II, and III, with 15 children in each group as follows: group I: probiotic mouthwash; group II: chlorhexidine mouthwash; and group III: sesame oil. Baseline scores of plaque index (PI) and modified gingival index (GI) were recorded followed by a full mouth oral prophylaxis. The designated mouth rinses were distributed to the respective groups and they were instructed to rinse once daily. Their parents supervised the children during the use of mouthwash. On the 15th and 30th day, the children were subjected to the same clinical measurements. Children's acceptance of their plaque control method was assessed using a modified facial image scale.

Results:
Intragroup comparisons for both the GI and PI scores were statistically significant ($p \leq 0.001$) in all the three groups. Difference in the GI scores between the 15th and 30th day was statistically significant for chlorhexidine group alone ($p = 0.024$). Intergroup comparisons between the three groups were not statistically significant.

Conclusion:
Probiotic mouthwash, chlorhexidine mouthwash, and sesame oil were equally effective in reducing plaque and in improving the gingival status of children. The difference between the gingival scores on the 15th and 30th day was statistically significant in the chlorhexidine group.

Indian J Dent Res. 2019 Jan-Feb;30(1):61-66. doi: 10.4103/ijdr.IJDR_247_17. (Open access available)

Effect of sugar-free chewing gum on plaque and gingivitis among 14-15-year-old school children: A randomized controlled trial.

Saheer PA, Parmar P, Majid SA, Bashyam M, Kousalya PS, Marriette TM.
India

AIM:
The aim of the study was to find out the effect of sugar-free chewing gums (xylitol and sorbitol) on plaque and gingivitis among 14-15-year-old school children.

MATERIALS AND METHODS:
A single center, double-blind, randomized controlled trial was conducted on 14-15-year-old children. Sample size was determined to be 48. **Participants were randomly allocated to test group (xylitol [n = 12], sorbitol [n = 12]) and control group (no gum, n = 24).** Duration of the study was 14 days. Baseline assessment of plaque, gingival, and bleeding score, followed by oral prophylaxis. Selected children received daily two chewing gum (1.1 g each) to chew for 20 min postbreakfast and postlunch. Follow-up was done on 15 day. Analysis was done using independent t-test, ANOVA, and post hoc test. Significance level was kept at $P < 0.05$.

RESULTS:
There was a significant reduction in plaque, gingival, and bleeding score in test group ($P < 0.05$) compared to control group.

CONCLUSION:
Sugar-free gum (xylitol and sorbitol) significantly reduced the plaque, gingival, and bleeding score.

Eur Arch Paediatr Dent. 2019 Mar 19. doi: 10.1007/s40368-019-00430-y.

A clinical and radiographic investigation comparing the efficacy of cast metal and indirect resin onlays in rehabilitation of permanent first molars affected with severe molar incisor hypomineralisation (MIH): a 36-month randomised controlled clinical trial.

Dhareula A, Goyal A, Gauba K, Bhatia SK, Kapur A, Bhandari S.
India

PURPOSE:
Definitive restorative management of young permanent molars affected with severe MIH is still elusive with a dearth of conservative restorative options. The present trial compared the 36 months clinical and radiographic performance of minimally invasive cast metal and indirect resin onlays for rehabilitation of permanent first molars affected with severe MIH.

METHODS:
In this parallel group open label randomised trial, 42 vital molars affected with severe MIH in 30 children, aged 8-13 years were randomly allocated using stratified permuted block randomization to receive either a cast metal onlay or an indirect composite onlay (n = 21 each). Clinical and radiographic evaluations of these onlays were carried out at 9, 18 and 36 months using the USPHS criteria. Cumulative survival rate as well as the calculated clinical success rates of both types of onlays were also determined. The longevity of onlays was assessed using Kaplan-Meier survival analysis.

RESULTS:
At 36 months, overall retention rate was found to be 95% with complete elimination of any pre-existing sensitivity. Cumulative survival rates were found to be 95% vs. 100%, p = 0.67, while the calculated clinical success rates were 90% and 85.7% for metal and resin onlays, respectively, with no significant differences (p = 0.76). Mean survival rates based on Kaplan-Meier analysis were determined to be 85% vs. 100% for the metal and composite groups, respectively (p = 0.075).

CONCLUSIONS:
Irrespective of the type of material used, onlays offer a predictable and conservative restorative alternative for molars affected with severe MIH.

Poisoning and toxins

(See envenomation)

Research

Perspect Clin Res. 2019 Apr-Jun;10(2):79-83. doi: 10.4103/picr.PICR_60_18. (Open access available)

The assessment of the quality of randomized controlled trials published in Indian medical journals.

Goenka L, Rajendran S, Arumugam K, Rani J, George M.
India

AIM:

In this retrospective cross-sectional study, we sought to evaluate if the published randomized controlled trials (RCTs) reported in the year 2017 among the Indian medical journals (IMJs) complied with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and identify domains where reporting could be improved.

METHODS:
A literature search was performed using PubMed and Google Scholar to identify all the IMJs that published RCTs in the year 2017. In the archives of the identified journals, the number of published RCTs was identified and the full text was obtained. We selected articles that stated RCT in abstract and title and that evaluated the safety and efficacy of all therapeutic and preventive interventions.

RESULTS:
A total of seven IMJs comprising of the Indian Journal of Anesthesia, Indian Journal of Dermatology, Venereology and Leprology, Indian Journal of Pharmacology, Indian Journal of Ophthalmology, Journal of Obstetrics and Gynaecology, Journal of Pharmacology and Pharmacotherapeutics, and Indian Journal of Medical and Pediatric Oncology that published a total of 84 RCTs were included. The mean compliance score of all the RCTs was 13.7 ± 2.66 (57%). **Most RCTs had serious reporting deficiencies in the methodology and result sections.**

DISCUSSION:
In spite of journals making it mandatory for prospective authors to comply with the CONSORT guidelines, it is intriguing that there continues to be significant lacunae in reporting RCTs adequately in most IMJs.

CONCLUSION:
There is an urgent need to impart training to the medical community of our country in clinical research methods and reporting of RCTs.

Quality of care

Schistosomiasis

PLoS Negl Trop Dis. 2019 Apr 10;13(4):e0007238. doi: 10.1371/journal.pntd.0007238. eCollection 2019 Apr. (Open access available)
Efficacy of China-made praziquantel for treatment of Schistosomiasis haematobium in Africa: A randomized controlled trial.
Wang XY, He J, Juma S, Kabole F, Guo JG, Dai JR, Li W, Yang K.
China, Zanzibar

BACKGROUND:

In the roadmap on the neglected tropical diseases (NTD) the World Health Organization (WHO) aims at attaining at least 75% coverage of preventive chemotherapy in pre-school and school-age children by 2020. A randomized controlled trial was used to compare the effectiveness of praziquantel in treating Schistosoma haematobium in Africa using two different sources for the drug, Merck Limited Partnership (KgaA), Germany and Nanjing Pharmaceutical Factory (NPF), China.

METHODS:
More than 6,000 participants testing positive for S. haematobium infection were enrolled from three villages (shehias) situated in the northern, middle and southern part of Pemba Island, Zanzibar. Applying criteria of inclusion and exclusion, resulted in a study population of 152 people (84 males, 68 females). A randomized controlled trial was conducted assigning participants to either praziquantel from NPF or Merck KGaA. After one month, the cure rate of S. haematobium and adverse events were compared to evaluate effectiveness. The ratio of male to female, the ratio of light/high infection intensity, and the average value of age were calculated between the two drug manufacturers. Chi-squared test and T-test were used for consistency analysis.

RESULTS:
Out of the total of 73 cases receiving praziquantel from NPF, the cure rate achieved was 97.3% (73/75), while the 74 cases receiving the drug from Merck KgaA reached a similar cure rate (96.1% or 74/77). There was no significant difference between the two outcomes ($\chi 2$ = 0.003, P = 0.956). Among the 75 patients treat, only one (a 16-years old female student), who had received the drug made in China had slight adverse reactions manifested as dizziness, headache and abdominal pain.

CONCLUSION:
The efficacy of China-made praziquantel does not differ significantly from praziquantel made by Merck KGaA in Germany.

School health and education

(See Adolescent health, Schistosomiasis)

Trials. 2018 Nov 29;19(1):664. doi: 10.1186/s13063-018-3043-3. (Open access available)

A cluster randomised trial of a classroom communication resource program to change peer attitudes towards children who stutter among grade 7 students.

Mallick R, Kathard H, Borhan ASM, Pillay M, Thabane L.
South Africa, Canada

BACKGROUND:
Classroom-based stuttering intervention addressing negative peer attitudes, perceptions, teasing and bullying of children who stutter (CWS) is required as part of holistic stuttering

management because of its occurrence in primary school. This study was conducted in 2017, in 10 primary schools in the Western Cape, South Africa within lower (second and third) and higher (fourth and fifth) quintiles.

OBJECTIVES:
The primary objective of this study was to determine treatment effect at six months after intervention of grade 7 participants (Classroom Communication Resource [CCR] intervention versus no CCR) using global **Stuttering Resource Outcomes Measure** (SROM) scores in school clusters. The secondary objective was to determine grade 7 participant treatment effect on the SROM subscales including Positive Social Distance (PSD), Social Pressure (SP) and Verbal Interaction (VI). The subgroup objective was to determine any difference in the primary outcome between schools between and across quintile clusters (lower and higher).

METHODS:
Once schools were stratified into lower and higher quintile (which are defined according to geographical location, fee per school and resources) subgroup clusters, schools were assigned randomly to control and intervention groups consisting of grade 7 participants who were typically aged ≥ 11 years. Teachers received 1 h of training before administering the single-dose CCR intervention over a 60-90-min session. The CCR intervention included a social story, role-play and discussion. All participants viewed a video of a CWS and stuttering was defined at baseline. The SROM measured peer attitudes at six months after intervention. Randomisation was stratified by quintile group using a 1:1 allocation ratio. Full blinding was not possible; however, the outcome assessor was partially blinded and the analyst was also blinded. Generalised estimating equations (GEE) was used assuming an exchangeable correlation structure to analyse the data adopting an intention-to-treat principle. Multiple imputation was used to handle missing data. Criterion for statistical significance was set at alpha = 0.05.

RESULTS:
Ten schools were randomly allocated to control (k = 5) and intervention groups (k = 5), with n = 223 participants allocated to intervention and n = 231 to control groups. A total of 454 participants completed the SROMs in control (n = 231) and intervention (n = 223) groups and were analysed at baseline and six months after intervention. **There was no statistically significant difference on the global SROM score (mean difference - 0.11; 95% confidence interval [CI] - 1.56-1.34; p = 0.88). There were also no significant differences on SROM subscales: PSD (mean difference 1.04; 95% CI - 1.02-311; p = 0.32), SP (mean difference - 0.45; 95% CI - 1.22-0.26; p = 0.21) and VI (mean difference 0.05; 95% CI - 1.01-1.11; p = 0.93).** Additionally, there was no significant subgroup effect on the global SROM score (lower versus higher quintile subgroups) (interaction p value = 0.52). No harms were noted or reported.

CONCLUSION:
No statistically significant differences were noted. It is possible that the time frame was too short to note changes in peer attitudes and that further study is required to confirm the findings of this study.

Lancet. 2018 Dec 8;392(10163):2465-2477. doi: 10.1016/S0140-6736(18)31615-5. Epub 2018 Nov 22.

Promoting school climate and health outcomes with the SEHER multi-component secondary school intervention in Bihar, India: a cluster-randomised controlled trial.

Shinde S, Weiss HA, Varghese B, Khandeparkar P, Pereira B, Sharma A, Gupta R, Ross DA, Patton G, Patel V.
UK, India, Australia, USA

BACKGROUND:
School environments affect health and academic outcomes. With increasing secondary school retention in low-income and middle-income countries, promoting quality school social environments could offer a scalable opportunity to improve adolescent health and wellbeing.

METHODS:
We did a cluster-randomised trial to assess the effectiveness of a multi-component whole-school health promotion intervention (SEHER) with integrated economic and process evaluations in grade 9 students (aged 13-14 years) at government-run secondary schools in the Nalanda district of Bihar state, India. **Schools were randomly assigned (1:1:1) to three groups: the SEHER intervention delivered by a lay counsellor (the SEHER Mitra [SM] group), the SEHER intervention delivered by a teacher (teacher as SEHER Mitra [TSM] group), and a control group in which only the standard government-run classroom-based life-skills Adolescence Education Program was implemented.** The primary outcome was school climate measured with the **Beyond Blue School Climate Questionnaire (BBSCQ).** Students were assessed at the start of the academic year (June, 2015) and again 8 months later at the end of the academic year (March, 2016) via self-completed questionnaires.

FINDINGS:
Of the 112 eligible schools in the Nalanda district, 75 were randomly selected to participate in the trial. **We randomly assigned 25 schools to each of the three groups.** One school subsequently dropped out of the TSM group, leaving 24 schools in this group. The baseline survey included a total of 13 035 participants, and the endpoint survey included 14 414 participants. **Participants in the SM-delivered intervention schools had substantially higher school climate scores at endpoint survey than those in the control group** (BBSCQ baseline-adjusted mean difference [aMD] 7·57 [95% CI 6·11-9·03]; effect size 1·88 [95% CI 1·44-2·32], p<0·0001) **and the TSM-delivered intervention** (aMD 7·57 [95% CI 6·06-9·08]; effect size 1·88 [95% CI 1·43-2·34], p<0·0001). **There was no effect of the TSM-delivered intervention compared with control** (aMD -0·009 [95% CI -1·53 to 1·51], effect size 0·00 [95% CI -0·45 to 0·44], p=0·99). Compared with the control group, participants in the SM-delivered intervention schools had moderate to large improvements in the secondary outcomes of depression (aMD -1·23 [95% CI -1·89 to -0·57]), bullying (aMD -0·91 [95% CI -1·15 to -0·66]), violence victimisation (odds ratio [OR] 0·62 [95% CI 0·46-0·84]), violence perpetration (OR 0·68 [95% CI 0·48-0·96]), attitude towards gender equity (aMD 0·41 [95% CI 0·21-0·61]), and

knowledge of reproductive and sexual health (aMD 0·29 [95% CI 0·06-0·53]). Similar results for these secondary outcomes were noted for the comparison between SM-delivered intervention schools and TSM-delivered intervention schools (depression: aMD -1·23 [95% CI -1·91 to -0·55]; bullying: aMD -0·83 [95% CI -1·08 to -0·57]; violence victimisation: OR 0·49 [95% CI 0·35-0·67]; violence perpetration: OR 0·49 [95% CI 0·34-0·71]; attitude towards gender equity: aMD 0·23 [95% CI 0·02-0·44]; and knowledge of reproductive and sexual health: aMD 0·22 [95% CI -0·02 to 0·47]). However, no effects on these secondary outcomes were observed for the TSM-delivered intervention schools compared with the control group (depression: aMD -0·03 [95% CI -0·70 to 0·65]; bullying: aMD -0·08 [95% CI -0·34 to 0·18]; violence victimisation: OR 1·27 [95% CI 0·93-1·73]; violence perpetration: OR 1·37 [95% CI 0·95-1·95]; attitude towards gender equity: aMD 0·17 [95% CI -0·09 to 0·38]; and knowledge of reproductive and sexual health: aMD 0·06 [95% CI -0·18 to 0·32]).

INTERPRETATION:
The multi-component whole-school SEHER health promotion intervention had substantial beneficial effects on school climate and health-related outcomes when delivered by lay counsellors, but no effects when delivered by teachers. Future research should focus on the evaluation of the scaling up of the SEHER intervention in diverse contexts and delivery agents.

Food Nutr Bull. 2018 Dec;39(4):595-607. doi: 10.1177/0379572118795358. Epub 2018 Nov 8. (Open access available)

Evaluation of the Effectiveness of a 3-Year, Teacher-Led Healthy Lifestyle Program on Eating Behaviors Among Adolescents Living in Day School Hostels in Malaysia.

Teng CY, Chin YS, Taib MNM, Chan YM.
Malaysia,

BACKGROUND:
Independence gained during adolescence may be associated with unhealthy eating behaviors. Although malnutrition among adolescents is evident, studies on eating behaviors among adolescents are scarce.

OBJECTIVE:
To determine the effectiveness of a teacher-led Healthy Lifestyle Program on eating behaviors among adolescents in Malaysia.

METHODS:
This was a cluster randomized controlled trial (conducted in 2012 to 2014), with 100 schools randomly selected from 721 schools, then assigned to 50 intervention schools and 50 control schools. A Healthy Eating and Be Active among Teens (HEBAT) module was developed for pretrained teachers to deliver a Healthy Lifestyle Program on eating behaviors among adolescents. Eating behaviors of the respondents was determined using Eating Behaviors

Questionnaire. Linear Mixed Model analysis and χ test were used to determine within- and between-group effects of studied variables.

RESULTS:
A total of 4277 respondents participated in this study, with 2635 samples involved in the final analysis, comprised of 921 intervention and 1714 control respondents. There were 32.4% (36.4%) males and 67.6% (63.6%) females in the intervention (control) group. Mean age was comparable between the groups (intervention = 12.98 years; control = 12.97 years). Majority of the respondents skipped meals at baseline (intervention = 74.7%; control = 79.5%). After the program, intervention respondents had higher consumption frequency of lunch, dinner, and mid-morning snack but a lower consumption frequency of late-evening snack and meal skipping behaviors than their control counterparts.

CONCLUSION:
The teacher-led Healthy Lifestyle Program was effective in reducing meal-skipping behaviors among Malaysian adolescents.

Am J Trop Med Hyg. 2018 Oct;99(4):924-933. doi: 10.4269/ajtmh.18-0187. (Open access available)

Effect of a School-Based Hygiene Behavior Change Campaign on Handwashing with Soap in Bihar, India: Cluster-Randomized Trial.

Lewis HE, Greenland K, Curtis V, Schmidt WP.
UK,

Abstract
Changing hand hygiene behavior at scale in the community remains a challenge. The objective of this study was to estimate the effect of Unilever's school-based "School of 5" handwashing campaign on handwashing with soap (HWWS) in schoolchildren and their mothers in the Indian state of Bihar. We conducted a cluster-randomized trial in two districts. **We randomized a total of 32 villages with at least one eligible school to intervention and control groups (1:1) and recruited 338 households in each group for outcome measurement.** We used structured observation in households to measure HWWS at target occasions (after defecation, soap use during bathing, and before each main meal) in schoolchildren and their mothers. Observers were blinded to intervention status. **We observed 636 target occasions (297 in the intervention arm and 339 in the control arm) in mothers and school-going children. After the intervention, HWWS prevalence at target occasions was 22.4% in the control arm and 26.6% in the intervention arm (prevalence difference +4.4%, 95% confidence interval: -4.0, 12.8).** The difference was similar in children and mothers. Observers appeared to be adequately blinded to intervention status, whereas observed households were successfully kept unaware of the purpose of observations. To conclude, we found no evidence for a health-relevant effect of the School of 5 intervention on HWWS in schoolchildren and their mothers. **Qualitative research suggested that reasons for the low impact of the intervention included low**

campaign intensity, ineffective delivery, and a model possibly not well tailored to these challenging physical and social environments.

Comment
No author from India listed

Saudi Med J. 2018 Oct;39(10):1044-1049. doi: 10.15537/smj.2018.10.23344. (Open access available)

The importance of hand hygiene education on primary schoolgirls' absence due to upper respiratory infections in Saudi Arabia. A cluster randomized controlled trial.

Alzaher AA, Almudarra SS, Mustafa MH, Gosadi IM.
Saudi Arabia

Abstract
To quantify the reduction in absence due to upper respiratory infections (URIs) among primary schoolgirls attending Riyadh's schools after delivering a hand hygiene workshop intervention over a period of 5 weeks. Methods: A cluster randomized trial was conducted among girls attending 4 primary schools between January and March 2018. The participants attended a hand hygiene workshop. The schoolgirls' absences were followed up for 5 weeks. Incidence rate, percentage of absence days, and absence rate were calculated for total and URIs absences. Result: Total number of participating schoolgirls was 496. Upper respiratory infections accounted for 15.3% of absence episodes. Schoolgirls lost 521 days of school and 19.4% of them were URIs-related. Absence rate due to URIs were 12.4 and 23.4 as well as 5.62 and 11.72 per 100 schoolgirls in the control (CG) and experimental (EG) groups, respectively. Percentage of absence days were lower in the experimental group (CG: 0.86% and 1.39% versus EG: 0.39% and 0.72%). Incidence rates of absence due to URIs were 0.54 and 1.02 in CG versus 0.24 and 0.51 in EG per 100 schoolgirls per day. Conclusion: There could be further reduction in school absences if education was accompanied by hand soap dissemination. The study could serve as a pilot for major studies in the future. Sustainability of the intervention can be tested in studies with longer durations.

Sepsis and serious bacterial infection

Cochrane Database Syst Rev. 2018 Nov 21;11:CD012125. doi: 10.1002/14651858.CD012125.pub2. (Open access available)

Corticosteroids for septic arthritis in children.

Delgado-Noguera MF, Forero Delgadillo JM, Franco AA, Vazquez JC, Calvache JA.
Colombia

BACKGROUND:

Septic arthritis is an acute infection of the joints characterised by erosive disruption of the articular space. It is the most common non-degenerative articular disease in developing countries. The most vulnerable population for septic arthritis includes infants and preschoolers, especially boys. Septic arthritis disproportionately affects populations of low socioeconomic status. Systemic corticosteroids and antibiotic therapy may be beneficial for treatment of septic arthritis. Even if the joint infection is eradicated by antibiotic treatment, the inflammatory process may produce residual joint damage and sequelae.

OBJECTIVES:
To determine the benefits and harms of corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis.

SEARCH METHODS:
We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, Latin American Caribbean Health Sciences Literature (LILACS), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/), ClinicalTrials.gov (www.ClinicalTrials.gov), and Google Scholar. We searched all databases from their inception to 17 April 2018, with no restrictions on language of publication.

SELECTION CRITERIA:
We included randomised controlled trials (RCTs) with patients from two months to 18 years of age with a diagnosis of septic arthritis who were receiving corticosteroids in addition to antibiotic therapy or as an adjuvant to other therapies such as surgical drainage, intra-articular puncture, arthroscopic irrigation, or debridement.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed eligibility, data extraction, and evaluation of risk of bias. We considered as major outcomes the presence of pain, activities of daily living, normal physical joint function, days of antibiotic treatment, length of hospital stay, and numbers of total and serious adverse events. We used standard methodological procedures expected by Cochrane. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created a 'Summary of findings' table.

MAIN RESULTS:
We included two RCTs involving a total of 149 children between three months and 18 years of age who were receiving antibiotics for septic arthritis. The most commonly affected joints were hips and knees. These studies were performed in Costa Rica and Israel. In both studies, dexamethasone administered intravenously (ranging from 0.15 to 0.2 mg/kg/dose every six to eight hours) during four days was the corticosteroid, and the comparator was placebo. Trials excluded patients with any degree of immunodeficiency or immunosuppression. The longest follow-up was one year. Trials did not report activities of daily living nor length of hospital stay. Both studies used adequate processes for randomisation, allocation concealment, and blinding, and review authors judged them to have low risk of selection and performance bias. Losses to follow-up were substantive in both studies, and we judged them to have high risk of attrition bias and of selective outcome reporting. We graded all outcomes as low quality due to concerns about study limitations and imprecision.The risk ratio (RR) for

absence of pain at 12 months of follow-up was 1.33, favouring corticosteroids (95% confidence interval (CI) 1.03 to 1.72; P = 0.03; number needed to treat for an additional beneficial outcome (NNTB) = 13, 95% CI 6 to 139; absolute risk difference 24%, 95% CI 5% to 43%). The RR for normal function of the affected joint at 12 months of follow-up was 1.32, favouring corticosteroids (95% CI 1.12 to 1.57; P = 0.001; NNTB = 13, 95% CI 7 to 33; absolute risk difference 24%, 95% CI 11% to 37%). We found a reduction in the number of days of intravenous antibiotic treatment favouring corticosteroids (mean difference (MD) -2.77, 95% CI -4.16 to -1.39) based on two trials with 149 participants. Researchers did not report length of hospital stay. One trial (49 participants) reported that treatment with dexamethasone was associated with a shorter duration of IV antibiotic treatment, leading to a shorter hospital stay, and although duration of hospitalisation was a primary outcome of the study, study authors did not provide data on the duration of hospitalisation. We downgraded the quality by one level for concerns about study limitations (high risk of attrition bias and selective reporting), and by another level for imprecision.In one trial of 49 participants, researchers followed 29 children for 12 months, and parents reported that no children demonstrated adverse effects of the intervention.

AUTHORS' CONCLUSIONS:
Evidence for corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis is of low quality and is derived from the findings of two trials (N = 149). Corticosteroids may increase the proportion of patients without pain and the proportion of patients with normal function of the affected joint at 12 months, and may also reduce the number of days of antibiotic treatment. However, we cannot draw strong conclusions based upon these trial results. Additional randomised clinical trials in children with relevant outcomes are needed.

Skin and hair disease

Pediatr Allergy Immunol. 2018 Dec;29(8):834-840. doi: 10.1111/pai.12978. Epub 2018 Sep 28.

The effects of melatonin administration on disease severity and sleep quality in children with atopic dermatitis: A randomized, double-blinded, placebo-controlled trial.

Taghavi Ardakani A, Farrehi M, Sharif MR, Ostadmohammadi V, Mirhosseini N, Kheirkhah D, Moosavi SGA, Behnejad M, Reiter RJ, Asemi Z.
Iran, Canada, USA

BACKGROUND:
The aim of this clinical trial was to determine the effects of melatonin administration on disease severity and sleep quality in children diagnosed with atopic dermatitis (AD).

METHODS:
This randomized, double-blinded, placebo-controlled trial was conducted by recruiting 70 patients, aged 6-12 years, who had been diagnosed with AD. Study participants were randomly allocated into two intervention groups to receive either 6 mg/d melatonin

supplements or placebo (n = 35 each group) for 6 weeks. Severity of disease was assessed using the scoring atopic dermatitis (SCORAD) and objective SCORAD indices. Sleep quality was evaluated by completing the Children's Sleep Habits Questionnaire (CSHQ).

RESULTS:
Following 6 weeks of intervention, melatonin supplementation significantly improved SCORAD index (β -3.55; 95% CI, -6.11, -0.98; P = 0.007), objective SCORAD index (β -3.23; 95% CI, -5.08, -1.38; P = 0.001), serum total IgE levels (β -153.94 ku/L; 95% CI, -260.39, -47.49; P = 0.005), and CSHQ scores (β -2.55; 95% CI, -4.34, -0.75; P = 0.006). However, melatonin had no significant impact on pruritus scores, high-sensitivity C-reactive protein (hs-CRP), sleep-onset latency, total sleep time, weight, and BMI compared with placebo.

CONCLUSIONS:
Overall, melatonin supplementation had beneficial effects on disease severity, serum total IgE levels, and CSHQ among children diagnosed with AD.

Snake bite and envenomation

Surgical problems

J Ayub Med Coll Abbottabad. 2018 Oct-Dec;30(4):520-523. (Open access available)

Comparison Of Simultaneous Versus Delayed Ventriculoperitoneal Shunting In Patients Undergoing Meningocoele Repair In Terms Of Infection.

Khattak HA, Gul N, Khan SA, Muhammad G, Aurangzeb A, Khan I.
Pakistan.

BACKGROUND:
Myelomeningocele is a congenital anomaly of Central Nervous System (CNS) leading to serious sequels related to various systems and organs of the affected patient. Hydrocephalus is a common condition associated with myelomeningocele. Hydrocephalus is seen in 11.8% of children with Myelomeningocele (MMC). This study was conducted to compare the simultaneous vs delayed ventriculoperitoneal shunting in children undergoing myelomeningocele in terms of infection.

METHODS:
This Randomized Control Trial was conducted at department of Neurosurgery, Ayub Medical College, Abbottabad from 7th March to 7th June 2016. In this study a total of 98 patients with MMC and hydrocephalus were randomly divided into two equal groups. In group A simultaneous MMC repair and VP shunting was performed while in group B MMC repair was done in first and VP shunting was done two weeks postoperatively.

RESULTS:
In this study mean age in Group A was 1 years with SD±2.77 while mean age in Group B was 1 years with SD±3.12. In Group A (12%) patients had infection and (88%) whereas in Group B (20%) patients had infection and (80%) patients didn't had infection.

CONCLUSIONS:
Simultaneous VP shunting was more effective than delayed VP shunting in children undergoing myelomeningocele in terms of infection.

J Neurosurg Pediatr. 2019 Jan 4;23(3):397-406. doi: 10.3171/2018.10.PEDS18354. (Open access available)

Infection risk for Bactiseal Universal Shunts versus Chhabra shunts in Ugandan infants: a randomized controlled trial.

Mbabazi-Kabachelor E, Shah M, Vaughan KA, Mugamba J, Ssenyonga P, Onen J, Nalule E, Kapur K, Warf BC.
Uganda, USA,

OBJECTIVE Clinical and economic repercussions of ventricular shunt infections are magnified in low-resource countries. The efficacy of antibiotic-impregnated shunts in this setting is unclear. A previous retrospective cohort study comparing the Bactiseal Universal Shunt (BUS) and the Chhabra shunt provided clinical equipoise; thus, the authors conducted this larger randomized controlled trial in Ugandan children requiring shunt placement for hydrocephalus to determine whether there was, in fact, any advantage of one shunt over the other. METHODS Between April 2013 and September 2016, the authors randomly assigned children younger than 16 years of age without evidence of ventriculitis to either BUS or Chhabra shunt implantation in this single-blind randomized controlled trial. The primary outcome was shunt infection, and secondary outcomes included reoperation and death. The minimum follow-up was 6 months. Time to outcome was assessed using the Kaplan-Meier method. The significance of differences was tested using Wilcoxon rank-sum, chi-square, Fisher's exact, and t-tests. RESULTS Of the 248 patients randomized, the BUS was implanted in 124 and the Chhabra shunt in 124. There were no differences between the groups in terms of age, sex, or hydrocephalus etiology. Within 6 months of follow-up, there were 14 infections (5.6%): 6 BUS (4.8%) and 8 Chhabra (6.5%; p = 0.58). There were 14 deaths (5.6%; 5 BUS [4.0%] vs 9 Chhabra [7.3%], p = 0.27) and 30 reoperations (12.1%; 15 BUS vs 15 Chhabra, p = 1.00). There were no significant differences in the time to primary or secondary outcomes at 6 months' follow-up (p = 0.29 and 0.17, respectively, Wilcoxon rank-sum test). CONCLUSIONS **Among Ugandan infants, BUS implantation did not result in a lower incidence of shunt infection or other complications.** Any recommendation for a more costly standard of care in low-resource countries must have contextually relevant, evidence-based support.

Training for health workers

Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

*** BMJ Open Respir Res. 2018 Oct 9;5(1):e000304. doi: 10.1136/bmjresp-2018-000304. eCollection 2018. (Open access available)

Incidence of tuberculosis and the influence of surveillance strategy on tuberculosis case-finding and all-cause mortality: a cluster randomised trial in Indian neonates vaccinated with BCG.

Jenum S, Selvam S, Jesuraj N, Ritz C, Hesseling AC, Cardenas V, Lau E, Doherty TM, Grewal HMS, Vaz M.
Norway, India, Denmark, South Africa, USA, Belgium

Introduction:
Accurate tuberculosis (TB) incidence and optimal surveillance strategies are pertinent to TB vaccine trial design. Infants are a targeted population for new TB vaccines, but data from India, with the highest global burden of TB cases, is limited.

Methods:
In a population-based prospective trial conducted between November 2006 and July 2008, BCG-vaccinated neonates in South India were enrolled and cluster-randomised to active or passive surveillance. **We assessed the influence of surveillance strategy on TB incidence, case-finding rates and all-cause mortality**. Predefined criteria were used to diagnose TB. All deaths were evaluated using a verbal autopsy.

Results:
4382 children contributed to 8164 person-years (py) of follow-up (loss to follow-up 6.9%); 749 children were admitted for TB evaluation (active surveillance: 641; passive surveillance: 108). The TB incidence was 159.2/100 000 py and the overall case-finding rate was 3.19 per 100 py (95% CI 0.82 to 18.1). Whereas, the case-finding rate for definite TB was similar using active or passive case finding, the case-finding rate for probable TB was 1.92/100 py (95% CI 0.83 to 3.78) with active surveillance, significantly higher than 0.3/100 py (95% CI 0.01 to 1.39, p=0.02) with passive surveillance. **Compared to passive surveillance, children with active surveillance had decreased risk of dying (OR 0.68, 95%CI 0.47 to 0.98) which was mostly attributable to reduction of death from pneumonia/respiratory infections (OR 0.34, 95%CI 0.14 to 0.80).**

Conclusion:
We provide reliable estimates of TB incidence in South Indian children <2 years of age. Active surveillance increased the case-finding rates for probable TB and was associated with reduced all-cause mortality.

Clin Infect Dis. 2019 May 24. pii: ciz436. doi: 10.1093/cid/ciz436. [Epub ahead of print]

Improving TPT Uptake: A Cluster-Randomized Trial of Symptom-Based Versus Tuberculin Skin Test-Based Screening of Household Tuberculosis Contacts Less than 5 Years of Age.

Salazar-Austin N[1], Cohn S[1], Barnes GL[1], Tladi M[2], Motlhaoleng K[2], Swanepoel C[3], Motala Z[3], Variava E[2,4], Martinson N[1,2], Chaisson RE[1].
USA, South Africa

BACKGROUND:
Tuberculosis preventive therapy(TPT) is highly-effective at preventing tuberculosis disease in household child contacts (<5 years), but is poorly implemented worldwide. In 2006, the World Health Organization recommended symptom-based screening as a replacement for tuberculin skin testing(TST) to simplify contact evaluation and improve implementation. We aimed to determine the effectiveness of this recommendation.
METHODS:
We conducted a pragmatic cluster-randomized trial to **determine whether contact evaluation using symptom screening improved the proportion of identified child contacts who initiated TPT compared to TST-based screening in Matlosana, South** Africa. Sixteen clinics were randomized to either symptom-based or TST-based contact evaluation. Outcome data were abstracted from customized child contact management files.
RESULTS:
Contact tracing identified 550 and 467 child contacts in the symptom and TST arms, respectively (0.39 vs 0.32 per case; p=0.27). There was no significant difference by arm in the adjusted proportion of identified child contacts who were screened (52% vs 60%; p=0.39). **The adjusted proportion of identified child contacts who initiated TPT or TB treatment was 51.5% in the symptom clinics and 57.1% in the TST clinics (difference -5.6%; 95%CI: -23.7-12.6; p=0.52).** Based on the district's historic average of 0.7 child contacts per index case, 14% and 15% of child contacts completed six-months of TPT in the two arms, respectively(p=0.89).
CONCLUSIONS:
Symptom-based screening did not improve the proportion of identified child contacts evaluated or initiated on TPT compared to TST-based screening. Further research is needed to identify bottlenecks and evaluate interventions to ensure all child contacts receive TPT

Engl J Med. 2018 Aug 2;379(5):454-463. doi: 10.1056/NEJMoa1714284. (Open access available)

Safety and Side Effects of Rifampin versus Isoniazid in Children.

Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, Obeng Baah J, Marks GB, Long R, Elwood K, Zielinski D, Gninafon M, Wulandari DA, Apriani L, Valiquette C, Fregonese F, Hornby K, Li PZ, Hill PC, Schwartzman K, Benedetti A, Menzies D.

Guinea, Canada, Indonesia, Brazil, Ghana, Australia, New Zealand

Abstract
BACKGROUND:
The treatment of latent infection with Mycobacterium tuberculosis is important in children because of their vulnerability to life-threatening forms of tuberculosis disease. **The current standard treatment - 9 months of isoniazid - has been associated with poor adherence and toxic effects, which have hampered the effectiveness of the drug.** In adults, treatment with 4 months of rifampin has been shown to be safer and to have higher completion rates than 9 months of isoniazid.

METHODS:
In this multicenter, open-label trial, we randomly assigned 844 children (<18 years of age) with latent M. tuberculosis infection to receive either 4 months of rifampin or 9 months of isoniazid. The primary outcome was adverse events of grade 1 to 5 that resulted in the permanent discontinuation of a trial drug. Secondary outcomes were treatment adherence, side-effect profile, and efficacy. Independent review panels whose members were unaware of trial-group assignments adjudicated all adverse events and progression to active tuberculosis.

RESULTS:
Of the children who underwent randomization, 829 were eligible for inclusion in the modified intention-to-treat analysis. A total of 360 of 422 children (85.3%) in the rifampin group completed per-protocol therapy, as compared with 311 of 407 (76.4%) in the isoniazid group (adjusted difference in the rates of treatment completion, 13.4 percentage points; 95% confidence interval [CI], 7.5 to 19.3). There were no significant between-group differences in the rates of adverse events, with fewer than 5% of the children in the combined groups with grade 1 or 2 adverse events that were deemed to be possibly related to a trial drug. Active tuberculosis, including 1 case with resistance to isoniazid, was diagnosed in 2 children in the isoniazid group during 542 person-years of follow-up, as compared with no cases in the rifampin group during 562 person-years (rate difference, -0.37 cases per 100 person-years; 95% CI, -0.88 to 0.14).

CONCLUSIONS:
Among children under the age of 18 years, treatment with 4 months of rifampin had similar rates of safety and efficacy but a better rate of adherence than 9 months of treatment with isoniazid.

Int J Tuberc Lung Dis. 2018 Dec 1;22(12):1422-1428. doi: 10.5588/ijtld.18.0168.

Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: a systematic review.

Hamada Y, Ford N, Schenkel K, Getahun H.
World Health Organization, Switzerland

BACKGROUND:
Uptake of preventive treatment for tuberculosis (TB) remains poor. **A 3-month regimen of rifapentine (RPT) plus isoniazid (INH) (3HP) could facilitate its scale-up.** We conducted a systematic review to assess the effects of 3HP compared with daily 6- or 9-month INH monotherapy.

METHODS:
We searched the following databases to identify randomised controlled trials: PubMed, Embase, the Web of Science, Cochrane Central Register of Controlled Trials, three ongoing trial registers and conference abstracts up to 24 January 2017. Where possible, we pooled data using a random-effects model.

RESULTS:
Four studies were included. Of those, we included two studies that compared 3HP with daily 6- or 9-month INH (6/9H) among adults with human immunodeficiency virus (HIV) co-infection, one among HIV-negative adults and one among predominantly HIV-negative children and adolescents. **Risk of active TB was not significantly different between 3HP and 6/9H** (risk ratio [RR] 0.73, 95%CI 0.23-2.29, in adults with HIV; RR 0.44, 95%CI 0.18-1.07, in adults without HIV; RR 0.13, 95%CI 0.01-2.54, in children and adolescents). **Risk of hepatotoxicity was significantly lower in the 3HP group among adults with HIV** (RR 0.26, 95%CI 0.12-0.55) and those without HIV (RR 0.16, 95%CI 0.10-0.27). **3HP was also associated with a higher completion rate in all subgroups.**

CONCLUSIONS:
HP was shown to have a preventive effect similar to that of INH monotherapy, with fewer adverse events and higher completion rates. 3HP can contribute significantly to the scale-up of preventive treatment.

BMC Infect Dis. 2019 Feb 4;19(1):110. doi: 10.1186/s12879-019-3738-4. (Open access available)

Test and Treat TB: a pilot trial of GeneXpert MTB/RIF screening on a mobile HIV testing unit in South Africa.

Bassett IV, Forman LS, Govere S, Thulare H, Frank SC, Mhlongo B, Losina E.
South Africa

BACKGROUND:
Community-based GeneXpert MTB/RIF testing may increase detection of prevalent TB in the community and improve rates of TB treatment completion.

METHODS:
We conducted a pilot randomized trial to evaluate the impact of GeneXpert screening on a mobile HIV testing unit. Adults (≥18y) underwent rapid HIV testing and TB symptom screening and were randomized to usual mobile unit care (providing sputum on the mobile unit sent out for GeneXpert testing) or the "Test & Treat TB" intervention with immediate

GeneXpert testing. Symptomatic participants in usual care produced sputum that was sent for hospital-based GeneXpert testing; participants were contacted ~ 7 days later with results. In the "Test & Treat TB" intervention, HIV-infected or HIV-uninfected/TB symptomatic participants underwent GeneXpert testing on the mobile unit. GeneXpert+ participants received expedited TB treatment initiation, monthly SMS reminders and non-cash incentives. We assessed 6-month TB treatment outcomes.

RESULTS:
4815 were eligible and enrolled; median age was 27 years (IQR 22 to 35). TB symptoms included cough (5%), weight loss (4%), night sweats (4%), and fever (3%). 42% of eligible participants produced sputum (intervention: 56%; usual care: 26%). Seven participants tested GeneXpert+, six in the intervention (3%, 95% CI 1%, 5%) and one in usual care (1%, 95% CI 0%, 6%). 5 of 6 intervention participants completed TB treatment; the GeneXpert+ participant in usual care did not.

CONCLUSION:
GeneXpert MTB/RIF screening on a mobile HIV testing unit is feasible. Yield for GeneXpert+ TB was low, however, the "Test & Treat TB" strategy led to high rates of TB treatment completion.

PLoS One. 2018 Sep 24;13(9):e0204554. doi: 10.1371/journal.pone.0204554. eCollection 2018. (Open access available)

C-Tb skin test to diagnose Mycobacterium tuberculosis infection in children and HIV-infected adults: A phase 3 trial.

Aggerbeck H, Ruhwald M, Hoff ST, Borregaard B, Hellstrom E, Malahleha M, Siebert M, Gani M, Seopela V, Diacon A, Lourens M, Andersen P, Dheda K.
Denmark, South Africa

BACKGROUND:
C-Tb, an ESAT-6/CFP-10-based skin test, has similar sensitivity for active TB compared to tuberculin skin test (TST) and QuantiFERON-TB-Gold-In-Tube (QFT). However, data are limited in children and HIV-infected persons.

METHODS:
Asymptomatic South African contacts <5 years (n = 87; HIV-uninfected), or symptomatic individuals of all ages presenting to clinics with suspected TB (n = 1003; 30% HIV-infected) were recruited from eight South African centres. C-Tb and TST were allocated to either forearm double blinded. Samples for QFT were collected in parallel, and test-positivity rates were compared.

RESULTS:
In participants with microbiologically confirmed TB (n = 75; 45% HIV-infected) sensitivity of C-Tb, TST and QFT were similar (72% versus 75% versus 73%; p>0.5). All 3 tests had similar positivity rates in HIV-infected participants with active TB, however, positivity rates were

reduced when CD4 counts were <100 cells/µL. In participants where active TB was excluded (n = 920), C-Tb (41%), TST (43%), and QFT (44%) also had similar test-positivity rates. Among asymptomatic contacts aged below five, 32% (28/87) tested positive with C-Tb and 32% (28/87) with TST (concordance 89%). Overall, C-Tb and TST showed a similar safety profile.

CONCLUSION:
C-Tb was safe and showed similar test-positivity rates, compared to TST and QFT, in children and HIV-infected persons with active or latent M. tuberculosis infection. These data inform the utility of C-Tb in clinical practice.

Typhus

Cochrane Database Syst Rev. 2018 Sep 24;9:CD002150. doi: 10.1002/14651858.CD002150.pub2. (Open access available)

Antibiotics for treating scrub typhus.

El Sayed I, Liu Q, Wee I, Hine P.
Egypt

BACKGROUND:
Scrub typhus, an important cause of acute fever in Asia, is caused by Orientia tsutsugamushi, an obligate intracellular bacterium. Antibiotics currently used to treat scrub typhus include tetracyclines, chloramphenicol, macrolides, and rifampicin.

OBJECTIVES:
To assess and compare the effects of different antibiotic regimens for treatment of scrub typhus.

SEARCH METHODS:
We searched the following databases up to 8 January 2018: the Cochrane Infectious Diseases Group specialized trials register; CENTRAL, in the Cochrane Library (2018, Issue 1); MEDLINE; Embase; LILACS; and the metaRegister of Controlled Trials (mRCT). We checked references and contacted study authors for additional data. We applied no language or date restrictions.

SELECTION CRITERIA:
Randomized controlled trials (RCTs) or quasi-RCTs comparing antibiotic regimens in people with the diagnosis of scrub typhus based on clinical symptoms and compatible laboratory tests (excluding the Weil-Felix test).

DATA COLLECTION AND ANALYSIS:
For this update, two review authors re-extracted all data and assessed the certainty of evidence. We meta-analysed data to calculate risk ratios (RRs) for dichotomous outcomes when appropriate, and elsewhere tabulated data to facilitate narrative analysis.

MAIN RESULTS:
We included six RCTs and one quasi-RCT with 548 participants; they took place in the Asia-Pacific region: Korea (three trials), Malaysia (one trial), and Thailand (three trials). **Only one trial included children younger than 15 years (N = 57).** We judged five trials to be at high risk of performance and detection bias owing to inadequate blinding. Trials were heterogenous in terms of dosing of interventions and outcome measures. Across trials, treatment failure rates were low.Two trials compared doxycycline to tetracycline. For treatment failure, the difference between doxycycline and tetracycline is uncertain (very low-certainty evidence). Doxycycline compared to tetracycline may make little or no difference in resolution of fever within 48 hours (risk ratio (RR) 1.14, 95% confidence interval (CI) 0.90 to 1.44, 55 participants; one trial; low-certainty evidence) and in time to defervescence (116 participants; one trial; low-certainty evidence). We were unable to extract data for other outcomes.Three trials compared doxycycline versus macrolides. For most outcomes, including treatment failure, resolution of fever within 48 hours, time to defervescence, and serious adverse events, we are uncertain whether study results show a difference between doxycycline and macrolides (very low-certainty evidence). Macrolides compared to doxycycline may make little or no difference in the proportion of patients with resolution of fever within five days (RR 1.05, 95% CI 0.99 to 1.10; 185 participants; two trials; low-certainty evidence). Another trial compared azithromycin versus doxycycline or chloramphenicol in children, but we were not able to disaggregate date for the doxycycline/chloramphenicol group.One trial compared doxycycline versus rifampicin. For all outcomes, we are uncertain whether study results show a difference between doxycycline and rifampicin (very low-certainty evidence). Of note, this trial deviated from the protocol after three out of eight patients who had received doxycycline and rifampicin combination therapy experienced treatment failure.Across trials, mild gastrointestinal side effects appeared to be more common with doxycycline than with comparator drugs.

AUTHORS' CONCLUSIONS:
Tetracycline, doxycycline, azithromycin, and rifampicin are effective treatment options for scrub typhus and have resulted in few treatment failures. Chloramphenicol also remains a treatment option, but we could not include this among direct comparisons in this review.Most available evidence is of low or very low certainty. For specific outcomes, some low-certainty evidence suggests there may be little or no difference between tetracycline, doxycycline, and azithromycin as treatment options. Given very low-certainty evidence for rifampicin and the risk of inducing resistance in undiagnosed tuberculosis, clinicians should not regard this as a first-line treatment option. Clinicians could consider rifampicin as a second-line treatment option after exclusion of active tuberculosis. Further research should consist of additional adequately powered trials of doxycycline versus azithromycin or other macrolides, trials of other candidate antibiotics including rifampicin, and trials of treatments for severe scrub typhus. Researchers should standardize diagnostic techniques and reporting of clinical outcomes to allow robust comparisons.

Urinary tract infection

Urology

Vaccines and immunization

(see also deworming)

Vaccine coverage and administration

Cochrane Database Syst Rev. 2018 Aug 9;8:CD010720. doi: 10.1002/14651858.CD010720.pub3. (Open access available)

Needle size for vaccination procedures in children and adolescents.

Beirne PV, Hennessy S, Cadogan SL, Shiely F, Fitzgerald T, MacLeod F.
Ireland

BACKGROUND:
This is an update of a Cochrane Review first published in 2015. The conclusions have not changed.Hypodermic needles of different sizes (gauges and lengths) can be used for vaccination procedures. The gauge (G) refers to the outside diameter of the needle tubing. The higher the gauge number, the smaller the diameter of the needle (e.g. a 23 G needle is 0.6 mm in diameter, whereas a 25 G needle is 0.5 mm in diameter). Many vaccines are recommended for injection into muscle (intramuscularly), although some are delivered subcutaneously (under the skin) and intradermally (into skin). Choosing an appropriate length and gauge of a needle may be important to ensure that a vaccine is delivered to the appropriate site and produces the maximum immune response while causing the least possible harm. Guidelines conflict regarding the sizes of needles that should be used for vaccinating children and adolescents.

OBJECTIVES:
To assess the effects of using needles of different sizes for administering vaccines to children and adolescents on vaccine immunogenicity (the ability of the vaccine to elicit an immune response), procedural pain, and other reactogenicity events (adverse events following vaccine administration).

SEARCH METHODS:
We updated our searches of CENTRAL, MEDLINE, Embase, and CINAHL to October 2017. We also searched proceedings of vaccine conferences and two trials registers.

SELECTION CRITERIA:
Randomised controlled trials evaluating the effects of using hypodermic needles of any gauge or length to administer any type of vaccine to people aged from birth to 24 years.

DATA COLLECTION AND ANALYSIS:
Three review authors independently extracted trial data and assessed the risk of bias. We contacted trial authors for additional information. We rated the quality of evidence using the GRADE system.

MAIN RESULTS:
We included five trials involving 1350 participants in the original review. The updated review identified no new trials. The evidence from two small trials (one trial including infants and one including adolescents) was insufficient to allow any definitive statements to be made about the effects of the needles evaluated in the trials on vaccine immunogenicity and reactogenicity.The remaining three trials (1135 participants) contributed data to comparisons between 25 G 25 mm, 23 G 25 mm, and 25 G 16 mm needles. These trials included infants predominantly aged from two to six months undergoing intramuscular vaccination in the anterolateral thigh using the World Health Organization (WHO) injection technique (skin stretched flat, needle inserted at a 90° angle and up to the needle hub in healthy infants). The vaccines administered were combination vaccines containing diphtheria, tetanus, and whole-cell pertussis antigens (DTwP). In some trials, the vaccines also contained Haemophilus influenzae type b (DTwP-Hib) and hepatitis B (DTwP-Hib-Hep B) antigen components.Primary outcomesIncidence of vaccine-preventable diseases: No trials reported this outcome.Procedural pain and crying: Using a wider gauge 23 G 25 mm needle may slightly reduce procedural pain (low-quality evidence) and probably leads to a slight reduction in the duration of crying time immediately after vaccination (moderate-quality evidence) compared with a narrower gauge 25 G 25 mm needle (one trial, 320 participants). The effects are probably not large enough to be clinically relevant.Secondary outcomesImmune response: There is probably little or no difference in immune response, defined in terms of the proportion of seroprotected infants, between use of 25 G 25 mm, 23 G 25 mm, or 25 G 16 mm needles to administer a series of three doses of a DTwP-Hib vaccine at ages two, three, and four months (moderate-quality evidence, one trial, numbers of participants in analyses range from 309 to 402. The immune response to the pertussis antigen was not measured).Severe and non-severe local reactions: 25 mm needles (either 25 G or 23 G) probably lead to fewer severe and non-severe local reactions after DTwP-Hib vaccination compared with 25 G 16 mm needles (moderate-quality evidence, one trial, 447 to 458 participants in analyses). We estimate that one fewer infant will experience a severe local reaction (extensive redness and swelling) after the first vaccine dose for every 25 infants vaccinated with the longer rather than the shorter needle (number needed to treat for an additional beneficial outcome (NNTB) with a 25 G 25 mm needle: 25 (95% confidence interval (CI) 15 to 100); NNTB with a 23 G 25 mm needle: 25 (95% CI 17 to 100)). We estimate that one fewer infant will experience a non-severe local reaction (any redness, swelling, tenderness, or hardness (composite outcome)) at 24 hours after the first vaccine dose for every 5 or 6 infants vaccinated with a 25 mm rather than a 16 mm needle (NNTB with a 25 G 25 mm needle: 5 (95% CI 4 to 10); NNTB with a 23 G 25 mm needle: 6 (95% CI 4 to 13)). The results are similar after the second and third vaccine doses.Using a narrow gauge 25 G 25 mm needle may produce a small reduction in the incidence of local reactions after each dose of a DTwP vaccine compared with a wider gauge 23 G 25 mm needle, but the effect estimates are imprecise (low-quality evidence, two trials, 100 to 459 participants in analyses).Systemic reactions: The comparative effects of 23 G 25 mm, 25 G 25 mm, and 25 G 16 mm needles on

the incidence of postvaccination fever and other systemic events such as drowsiness, loss of appetite, and vomiting are uncertain due to the very low quality of the evidence.

AUTHORS' CONCLUSIONS:
Using 25 mm needles (either 23 G or 25 G) for intramuscular vaccination procedures in the anterolateral thigh of infants using the WHO injection technique probably reduces the occurrence of local reactions while achieving a comparable immune response to 25 G 16 mm needles. These findings are applicable to healthy infants aged two to six months receiving combination DTwP vaccines with a reactogenic whole-cell pertussis antigen component. These vaccines are predominantly used in low- and middle-income countries. The applicability of the findings to vaccines with acellular pertussis components and other vaccines with different reactogenicity profiles is uncertain.

Vaccine-related adverse effects

BCG vaccine

(See also Vaccine - Tuberculosis vaccine)

N Engl J Med. 2018 Jul 12;379(2):138-149. doi: 10.1056/NEJMoa1714021. (Open access available)

Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination.

Nemes E, Geldenhuys H, Rozot V, Rutkowski KT, Ratangee F, Bilek N, Mabwe S, Makhethe L, Erasmus M, Toefy A, Mulenga H, Hanekom WA, Self SG, Bekker LG, Ryall R, Gurunathan S, DiazGranados CA, Andersen P, Kromann I, Evans T, Ellis RD, Landry B, Hokey DA, Hopkins R, Ginsberg AM, Scriba TJ, Hatherill M; C-040-404 Study Team.
South African, Denmark

BACKGROUND:
Recent Mycobacterium tuberculosis infection confers a predisposition to the development of tuberculosis disease, the leading killer among global infectious diseases. H4:IC31, a candidate subunit vaccine, has shown protection against tuberculosis disease in preclinical models, and observational studies have indicated that primary bacille Calmette-Guérin (BCG) vaccination may offer partial protection against infection.

METHODS:
In this phase 2 trial, we randomly assigned 990 adolescents in a high-risk setting who had undergone neonatal BCG vaccination to receive the H4:IC31 vaccine, BCG revaccination, or placebo. All the participants had negative results on testing for M. tuberculosis infection on the QuantiFERON-TB Gold In-tube assay (QFT) and for the human immunodeficiency virus. The primary outcomes were safety and acquisition of M. tuberculosis infection, as defined by initial conversion on QFT that was performed every 6 months during a 2-year period. Secondary outcomes were immunogenicity and sustained QFT conversion to a positive test

without reversion to negative status at 3 months and 6 months after conversion. Estimates of vaccine efficacy are based on hazard ratios from Cox regression models and compare each vaccine with placebo.

RESULTS:
Both the BCG and H4:IC31 vaccines were immunogenic. QFT conversion occurred in 44 of 308 participants (14.3%) in the H4:IC31 group and in 41 of 312 participants (13.1%) in the BCG group, as compared with 49 of 310 participants (15.8%) in the placebo group; the rate of sustained conversion was 8.1% in the H4:IC31 group and 6.7% in the BCG group, as compared with 11.6% in the placebo group. Neither the H4:IC31 vaccine nor the BCG vaccine prevented initial QFT conversion, with efficacy point estimates of 9.4% (P=0.63) and 20.1% (P=0.29), respectively. However, the BCG vaccine reduced the rate of sustained QFT conversion, with an efficacy of 45.4% (P=0.03); the efficacy of the H4:IC31 vaccine was 30.5% (P=0.16). There were no clinically significant between-group differences in the rates of serious adverse events, although mild-to-moderate injection-site reactions were more common with BCG revaccination.

CONCLUSIONS:
In this trial, the rate of sustained QFT conversion, which may reflect sustained M. tuberculosis infection, was reduced by vaccination in a high-transmission setting. This finding may inform clinical development of new vaccine candidates.

Pediatr Infect Dis J. 2019 Feb;38(2):198-202. doi: 10.1097/INF.0000000000002198.

Two Randomized Trials of the Effect of the Russian Strain of Bacillus Calmette-Guérin Alone or With Oral Polio Vaccine on Neonatal Mortality in Infants Weighing <2000 g in India.

Jayaraman K, Adhisivam B, Nallasivan S, Krishnan RG, Kamalarathnam C, Bharathi M, McSharry B, Namachivayam SP, Shann F, Boopalan SI, David P, Bhat BV.
India, New Zealand, Australia

BACKGROUND:
In randomized trials in Guinea-Bissau, the Danish strain of Bacillus Calmette-Guérin (BCG) reduces neonatal mortality, primarily by reducing deaths from pneumonia and sepsis. Because World Health Organization-prequalified BCG-Denmark was not available in India, we conducted 2 randomized trials to test whether BCG-Russia alone or with oral polio vaccine (OPV) has similar effects to BCG-Denmark.

METHODS:
We randomized neonates weighing <2000 g to a control group that was not vaccinated before 28 days of age or to receive either BCG-Russia alone (first trial) or BCG-Russia with OPV (second trial) soon after birth. We performed intention-to-treat analysis using Cox hazards models with age as the underlying time and adjusted for weight, sex and inborn versus outborn status.

RESULTS:
Administration of BCG-Russia alone had no effect on neonatal mortality (to 28 days of age): 15.6% of 1537 infants died in the BCG-Russia group and 16.1% of 1535 died in the control group; the adjusted hazard ratio was 0.95 [95% confidence interval (CI): 0.80-1.13]. Administration of BCG-Russia with OPV also had no effect on neonatal mortality: 18.0% of 1103 infants died in the BCG-OPV group and 17.6% of 1104 died in the control group; the adjusted hazard ratio was 1.01 (95% CI: 0.83-1.23). The adjusted hazard ratio for the 2 trials combined was 0.98 (95% CI: 0.85-1.11).

CONCLUSIONS:
BCG-Russia with or without OPV had no effect on neonatal mortality. It is important to determine which strains of BCG have the greatest specific effects (on tuberculosis) and nonspecific effects (on infections other than tuberculosis) in high-mortality regions.

Cholera vaccine

Dengue vaccine

Ebola vaccine

Enterovirus 71 vaccine

Hepatitis A vaccine

Hepatitis B vaccine

HIV vaccine

HPV vaccine

Influenza vaccine

Clin Infect Dis. 2019 Jan 28. doi: 10.1093/cid/ciz066. [Epub ahead of print] (Open access available)

Effectiveness of seasonal influenza vaccination of children in Senegal during a year of vaccine mismatch: a cluster-randomized trial.

Diallo A, Diop OM, Diop D, Niang MN, Sugimoto JD, Ortiz JR, Faye EHA, Diarra B, Goudiaby D, Lewis KDC, Emery SL, Zangeneh SZ, Lafond KE, Sokhna C, Halloran ME, Widdowson MA, Neuzil KM, Victor JC.
Senegal, USA

Background:
Population effects of influenza vaccination of children have not been extensively studied, especially in tropical developing countries. In rural Senegal, we assessed the total (primary objective) and indirect effectiveness of inactivated influenza vaccine, trivalent (IIV3).

Methods:
In this double-blind, cluster-randomized trial, villages were randomly allocated (1:1) for high-coverage vaccination of children aged 6 months through 10 years with 2008-09 northern hemisphere IIV3 or inactivated polio vaccine (IPV). Vaccinees were monitored for serious adverse events. All village residents, vaccinated and unvaccinated, were monitored for signs and symptoms of influenza illness using weekly home visits and surveillance in designated clinics. The primary outcome was all laboratory-confirmed symptomatic influenza.

Results:
Between May 23 and July 11, 2009, **20 villages were randomized, and 66.5% of age-eligible children were enrolled** (3918 in IIV3 villages and 3848 in IPV villages). Follow-up continued until May 28, 2010. Four unrelated serious adverse events were identified. **Among vaccinees, total effectiveness against illness caused by seasonal influenza virus (presumed all drifted A/H3N2 based on antigenic characterization data) circulating at high rates among children was 43.6% (95% CI, 18.6% to 60.9%).** Indirect effectiveness against seasonal A/H3N2 was 15.4% (95% CI, -22.0% to 41.3%). Total effectiveness against illness caused by pandemic influenza virus (A/H1N1pdm09) was -52.1% (95% CI, -177.2% to 16.6%).

Conclusions:
IIV3 provided statistically significant, moderate protection to children in Senegal against circulating pre-2010 seasonal influenza strains but not against A/H1N1pdm09 not included in the vaccine. No indirect effects were measured. Further study in low resource populations is warranted.

Lancet Child Adolesc Health. 2018 May;2(5):338-349. doi: 10.1016/S2352-4642(18)30062-2. Epub 2018 Mar 5.

Prevention of vaccine-matched and mismatched influenza in children aged 6-35 months: a multinational randomised trial across five influenza seasons.

Claeys C, Zaman K, Dbaibo G, Li P, Izu A, Kosalaraksa P, Rivera L, Acosta B, Arroba Basanta ML, Aziz A, Cabanero MA, Chandrashekaran V, Corsaro B, Cousin L, Diaz A, Diez-Domingo J, Dinleyici EC, Faust SN, Friel D, Garcia-Sicilia J, Gomez-Go GD, Antoinette Gonzales ML, Hughes SM, Jackowska T, Kant S, Lucero M, Malvaux L, Mares Bermudez J, Martinon-Torres F, Miranda M, Montellano M, Peix Sambola MA, Prymula R, Puthanakit T, Ruzkova R, Sadowska-Krawczenko I, Salamanca de la Cueva I, Sokal E, Soni J, Szymanski H, Ulied A, Schuind A, Jain VK, Innis BL; Flu4VEC Study Group.

Belgium, Bangladesh, Lebanon, USA, Thailand, Dominican Republic, Spain, Honduras, Turkey, Philippines, UK, Poland, India, Czech Republic, India

BACKGROUND:
Despite the importance of vaccinating children younger than 5 years, few studies evaluating vaccine prevention of influenza have been reported in this age group. We evaluated efficacy of an inactivated quadrivalent influenza vaccine (IIV4) in children aged 6-35 months.

METHODS:
In this phase 3, observer-blinded, multinational trial, healthy children from 13 countries in Europe, Central America, and Asia were recruited in five independent cohorts, each in a different influenza season. **Participants were randomly assigned (1:1) to either IIV4 (15 µg haemagglutinin antigen per strain per 0·5 mL dose; a single dose on day 0 for vaccine-primed children, and two doses, on days 0 and 28, for vaccine-unprimed children) or to one or two doses of a non-influenza control vaccine.** Primary endpoints were moderate-to-severe influenza or all influenza (irrespective of disease severity) confirmed by RT-PCR on nasal swabs. Cultured isolates were further characterised as antigenically matched or mismatched to vaccine strains. Efficacy was assessed in the per-protocol cohort and total vaccinated cohort (time-to-event analysis), and safety was assessed in the total vaccinated cohort.

FINDINGS:
Between Oct 1, 2011, and Dec 31, 2014, 12 018 children were recruited into the total vaccinated cohort (6006 children in the IIV4 group and 6012 children in the control group). 356 (6%) children in the IIV4 group and 693 (12%) children in the control group had at least one case of RT-PCR-confirmed influenza. Of these 1049 influenza strains, 138 (13%) were A/H1N1, 529 (50%) were A/H3N2, 69 (7%) were B/Victoria, and 316 (30%) were B/Yamagata. Overall, 539 (64%) of 848 antigenically characterised isolates were vaccine-mismatched (16 [15%] of 105 for A/H1N1; 368 [97%] of 378 for A/H3N2; 54 [86%] of 63 for B/Victoria; 101 [33%] of 302 for B/Yamagata). Vaccine efficacy was 63% (97·5% CI 52-72) against moderate-to-severe influenza and 50% (42-57) against all influenza in the per-protocol cohort, and 64% (53-73) against moderate-to-severe influenza and 50% (42-57) against all influenza in the total vaccinated cohort. There were no clinically meaningful safety differences between IIV4 and control.

INTERPRETATION:
IIV4 prevented influenza A and B in children aged 6-35 months despite high levels of vaccine mismatch. Vaccine efficacy was highest against moderate-to-severe disease, which is the most clinically important endpoint associated with greatest burden.

Vaccine. 2019 Mar 22;37(13):1876-1884. doi: 10.1016/j.vaccine.2018.11.074. Epub 2018 Dec 14. (Open access available)

Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6-35 months: A multi-season randomised placebo-controlled trial in the Northern and Southern Hemispheres.

Pepin S, Dupuy M, Borja-Tabora CFC, Montellano M, Bravo L, Santos J, de Castro JA, Rivera-Medina DM, Cutland C, Ariza M, Diez-Domingo J, Gonzalez CD, Martinón-Torres F, Papadopoulou-Alataki E, Theodoriadou M, Kazek-Duret MP, Gurunathan S, De Bruijn I; GQM05 Study Group.
France, Philippines, Honduras, South Africa, Spain, Greece, USA,

BACKGROUND:
A quadrivalent split-virion inactivated influenza vaccine (VaxigripTetra™, Sanofi Pasteur; IIV4) containing two A strains (H1N1 and H3N2) and B strains from both lineages (Victoria and Yamagata) was approved in Europe in 2016 for individuals aged ≥ 3 years. This study examined the efficacy and safety of IIV4 in children aged 6-35 months.

METHODS:
This was a phase III randomised controlled trial conducted in Latin America, Asia, Africa, and Europe during the Northern Hemisphere 2014/2015 and 2015/2016 and Southern Hemisphere 2014 and 2015 influenza seasons. Healthy children aged 6-35 months not previously vaccinated against influenza were randomised to receive two full doses 28 days apart of IIV4, placebo, the licensed trivalent split-virion inactivated vaccine (IIV3), an investigational IIV3 containing a B strain from the alternate lineage. The primary objective was to demonstrate efficacy against influenza illness caused by any strain or vaccine-similar strains.

RESULTS:
The study enrolled 5806 participants. Efficacy, assessed in 4980 participants completing the study according to protocol, was demonstrated for IIV4. **Vaccine efficacy was 50.98% (97% CI, 37.36-61.86%) against influenza caused by any A or B type and 68.40% (97% CI, 47.07-81.92%) against influenza caused by vaccine-like strains.** Safety profiles were similar for IIV4, placebo, and the IIV3s, although injection-site reactions were slightly more frequent for IIV4 than placebo.

CONCLUSIONS:
IIV4 was safe and effective for protecting children aged 6-35 months against influenza illness caused by vaccine-similar or any circulating strains.

Vaccine. 2018 Oct 15;36(43):6424-6432. doi: 10.1016/j.vaccine.2018.08.032. Epub 2018 Sep 14. (Open access available)

Immunogenicity and safety of MF59-adjuvanted and full-dose unadjuvanted trivalent inactivated influenza vaccines among vaccine-naïve children in a randomized clinical trial in rural Senegal.

Diallo A, Victor JC, Feser J, Ortiz JR, Kanesa-Thasan N, Ndiaye M, Diarra B, Cheikh S, Diene D, Ndiaye T, Ndiaye A, Lafond KE, Widdowson MA, Neuzil KM.
Author information

Randomised trials in child health in developing countries 2018-19

Senegal, USA,

INTRODUCTION:
Effective, programmatically suitable influenza vaccines are needed for low-resource countries.

MATERIALS AND METHODS:
This phase II, placebo-controlled, randomized safety and immunogenicity trial (NCT01819155) was conducted in Senegal using the 2012-2013 Northern Hemisphere trivalent influenza vaccine (TIV) formulation. Participants were allocated in a 2:2:1 ratio to receive TIV (full-dose for all age groups), adjuvanted TIV (aTIV), or placebo. Participants were stratified into age groups: 6-11, 12-35, and 36-71 months. All participants were vaccine-naïve and received two doses of study vaccine 4 weeks apart. The two independent primary objectives were to estimate the immunogenicity of TIV and of aTIV as the proportion of children with a hemagglutination inhibition (HI) antibody titer of ≥1:40 to each vaccine strain at 28 days post-dose two. Safety was evaluated by solicited local and systemic reactions, unsolicited adverse events, and serious adverse events.

RESULTS:
296 children received TIV, aTIV, or placebo, and 235 were included in the final analysis. After two doses, children aged 6-11, 12-35, and 36-71 months receiving TIV had HI titers ≥1:40 against A/H1N1 (73.1%, 94.1%, and 97.0%), A/H3N2 (96.2%, 100.0%, and 100.0%), and B (80.8%, 97.1%, and 97.0%), respectively. After two doses, 100% children aged 6-11, 12-35, and 36-71 months receiving aTIV had ≥1:40 titers against A/H1N1, A/H3N2, and B. After a single dose, the aTIV response was comparable to or greater than the TIV response for all vaccine strains. TIV and aTIV reactogenicity were similar, except for mild elevation in temperature (37.5-38.4 °C) which occurred more frequently in aTIV than TIV after each vaccine dose. TIV and aTIV had similarly increased pain/tenderness at the injection site compared to placebo.

CONCLUSIONS:
Both aTIV and full-dose TIV were well-tolerated and immunogenic in children aged 6-71 months. These vaccines may play a role in programmatically suitable strategies to prevent influenza in low-resource settings.

Japanese encephalitis virus vaccine

Malaria vaccine

Hum Vaccin Immunother. 2019 Apr 23:1-13. doi: 10.1080/21645515.2019.1586040. [Epub ahead of print] (Open access available)

Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa.

Guerra Mendoza Y, Garric E, Leach A, Lievens M, Ofori-Anyinam O, Pirçon JY, Stegmann JU, Vandoolaeghe P, Otieno L, Otieno W, Owusu-Agyei S, Sacarlal J, Masoud NS, Sorgho H, Tanner M, Tinto H, Valea I, Mtoro AT, Njuguna P, Oneko M, Otieno GA, Otieno K, Gesase S, Hamel MJ, Hoffman I, Kaali S, Kamthunzi P, Kremsner P, Lanaspa M, Lell B, Lusingu J, Malabeja A, Aide P, Akoo P, Ansong D, Asante KP, Berkley JA, Adjei S, Agbenyega T, Agnandji ST, Schuerman L.

Abstract
A phase III, double-blind, randomized, controlled trial (NCT00866619) in sub-Saharan Africa showed RTS,S/AS01 vaccine efficacy against malaria. We now present in-depth safety results from this study. **8922 children (enrolled at 5-17 months) and 6537 infants (enrolled at 6-12 weeks) were 1:1:1-randomized to receive 4 doses of RTS,S/AS01 (R3R) or non-malaria control vaccine (C3C), or 3 RTS,S/AS01 doses plus control (R3C).** Aggregate safety data were reviewed by a multi-functional team. Severe malaria with Blantyre Coma Score ≤2 (cerebral malaria [CM]) and gender-specific mortality were assessed post-hoc. Serious adverse event (SAE) and fatal SAE incidences throughout the study were 24.2%-28.4% and 1.5%-2.5%, respectively across groups; 0.0%-0.3% of participants reported vaccination-related SAEs. **The incidence of febrile convulsions in children was higher during the first 2-3 days post-vaccination with RTS,S/AS01 than with control vaccine, consistent with the time window of post-vaccination febrile reactions in this study (mostly the day after vaccination).** A statistically significant numerical imbalance was observed for meningitis cases in children (R3R: 11, R3C: 10, C3C: 1) but not in infants. CM cases were more frequent in RTS,S/AS01-vaccinated children (R3R: 19, R3C: 24, C3C: 10) but not in infants. **All-cause mortality was higher in RTS,S/AS01-vaccinated versus control girls (2.4% vs 1.3%, all ages) in our setting with low overall mortality. The observed meningitis and CM signals are considered likely chance findings, that - given their severity - warrant further evaluation in phase IV studies and WHO-led pilot implementation programs to establish the RTS,S/AS01 benefit-risk profile in real-life settings.**

PLoS One. 2018 Dec 31;13(12):e0209744. doi: 10.1371/journal.pone.0209744. eCollection 2018. (Open access available)

Current challenges and proposed solutions to the effective implementation of the RTS, S/AS01 Malaria Vaccine Program in sub-Saharan Africa: A systematic review.

Dimala CA, Kika BT, Kadia BM, Blencowe H
UK, Camaroon, Belgium

BACKGROUND:
The Malaria Vaccine Implementation Program, coordinated by the World Health Organization, intended to initiate the roll-out of the RTS, S/AS01 malaria vaccine in 3 sub-

Saharan African countries in 2018. **With sub-optimal implementation, the effectiveness of this vaccine in routine clinical use could be significantly lower than its measured efficacy in randomized trials.** This study had as objectives to systematically review and summarize published studies addressing the challenges faced during the implementation phase of malaria vaccination programs and randomized trials conducted in sub-Saharan Africa. The review also sought to report proposed solutions to the challenges identified.

METHOD:
This was a systematic review of studies published between 1947 and 2017. Medline, Embase and the Cochrane library databases were searched. Of the 365 studies retrieved, 8 eligible studies reported on challenges of implementing a malaria vaccine in sub-Saharan Africa and possible solutions to these challenges. Data were abstracted from the eligible studies and a qualitative synthesis was done.

RESULTS:
The 8 studies included in the review had a total of 6189 participants and used a variety of methodologies (3 qualitative, 1 quantitative, 3 mixed method studies and 1 clinical trial review). There was an overall positive acceptance towards the new malaria vaccine (n = 6/8 studies), with a mean acceptance rate of 86.1% (95% CI: 62.0-110.2, n = 2). The main challenges to vaccine receptivity were: inadequate community engagement due to lack of information about the vaccine (n = 6), fear of the vaccine's side effects (n = 5), inefficient delivery of vaccination services to children (n = 4), and sub-optimal quality of the health services (n = 3). Main themes identified from the proposed solutions consisted of the following: using dynamic communication models and trusted sources for delivering vaccine-related health information to the communities (n = 6), community engagement at both national and district level (n = 6), implementing the new vaccine services alongside the existing health services already delivered (n = 6).

CONCLUSION/RECOMMENDATIONS:
Effective implementation of the malaria vaccine program requires careful consideration of the socio-cultural context of each community. The RTS, S/AS01 malaria vaccine acceptance and uptake may be significantly enhanced if caregivers' perceptions about vaccines and their importance are adequately fine-tuned. In order to achieve these, community participation and the provision of adequate information in an acceptable form via reliable communication channels seem to be imperative.

PLoS One. 2018 Dec 12;13(12):e0208328. doi: 10.1371/journal.pone.0208328. eCollection 2018. (Open access available)

First field efficacy trial of the ChAd63 MVA ME-TRAP vectored malaria vaccine candidate in 5-17 months old infants and children.

Tiono AB, Nébié I, Anagnostou N, Coulibaly AS, Bowyer G, Lam E, Bougouma EC, Ouedraogo A, Yaro JBB, Barry A, Roberts R, Rampling T, Bliss C, Hodgson S, Lawrie A, Ouedraogo A, Imoukhuede EB, Ewer KJ, Viebig NK, Diarra A, Leroy O, Bejon P, Hill AVS, Sirima SB.
Burkina Faso, United Kingdom, Germany, Kenya

BACKGROUND:
Heterologous prime boost immunization with chimpanzee adenovirus 63 (ChAd63) and Modified Vaccinia Virus Ankara (MVA) vectored vaccines is a strategy previously shown to provide substantial protective efficacy against P. falciparum infection in United Kingdom adult Phase IIa sporozoite challenge studies (approximately 20-25% sterile protection with similar numbers showing clear delay in time to patency), and greater point efficacy in a trial in Kenyan adults.

METHODOLOGY:
We conducted the first Phase IIb clinical trial assessing the safety, immunogenicity and efficacy of ChAd63 MVA ME-TRAP in 700 healthy malaria exposed children aged 5-17 months in a highly endemic malaria transmission area of Burkina Faso.
RESULTS:
ChAd63 MVA ME-TRAP was shown to be safe and immunogenic but induced only moderate T cell responses (median 326 SFU/106 PBMC (95% CI 290-387)) many fold lower than in previous trials. No significant efficacy was observed against clinical malaria during the follow up period, with efficacy against the primary endpoint estimate by proportional analysis being 13.8% (95%CI -42.4 to 47.9) at sixth month post MVA ME-TRAP and 3.1% (95%CI -15.0 to 18.3; p = 0.72) by Cox regression.
CONCLUSIONS:
This study has confirmed ChAd63 MVA ME-TRAP is a safe and immunogenic vaccine regimen in children and infants with prior exposure to malaria. But no significant protective efficacy was observed in this very highly malaria-endemic setting.

Measles vaccine

Lancet Infect Dis. 2019 Apr;19(4):402-409. doi: 10.1016/S1473-3099(18)30650-9. Epub 2019 Mar 1. (Open access available)

Immunogenicity and safety of measles-rubella vaccine co-administered with attenuated Japanese encephalitis SA 14-14-2 vaccine in infantsaged 8 months in China: a non-inferiority randomised controlled trial.

Li Y, Chu SY, Yue C, Wannemuehler K, Xie S, Zhang F, Wang Y, Zhang Y, Ma R, Li Y, Zuo Z, Rodewald L, Xiao Q, Feng Z, Wang H, An Z.
China

BACKGROUND:
In China, measles-rubella vaccine and live attenuated SA 14-14-2 Japanese encephalitis vaccine (LJEV) are recommended for simultaneous administration at 8 months of age, which is the youngest recommended age for these vaccines worldwide. We aimed to assess the effect of the co-administration of these vaccines at 8 months of age on the immunogenicity of measles-rubella vaccine.

METHODS:

We did a multicentre, open-label, non-inferiority, two-group randomised controlled trial in eight counties or districts in China. We recruited healthy infants aged 8 months who had received all scheduled vaccinations according to the national immunisation recommendations and who lived in the county of the study site. Enrolled infants were randomly assigned (1:1) to receive either measles-rubella vaccine and LJEV simultaneously (measles-rubella plus LJEV group) or measles-rubella vaccine alone (measles-rubella group). The primary outcome was the proportion of infants with IgG antibody seroconversion for measles 6 weeks after vaccination, and a secondary outcome was the proportion of infants with IgG antibody seroconversion for rubella 6 weeks after vaccination. Analyses included all infants who completed the study. We used a 5% margin to establish non-inferiority. This trial was registered at ClinicalTrials.gov (NCT02643433).

FINDINGS:
1173 infants were assessed for eligibility between Aug 13, 2015, and June 10, 2016. Of 1093 (93%) enrolled infants, 545 were randomly assigned to the measles-rubella plus LJEV group and 548 to the measles-rubella group. Of the infants assigned to each group, 507 in the measles-rubella plus LJEV group and 506 in the measles-rubella group completed the study. Before vaccination, six (1%) of 507 infants in the measles-rubella plus LJEV group and one (<1%) of 506 in the measles-rubella group were seropositive for measles; eight (2%) infants in the measles-rubella plus LJEV group and two (<1%) in the measles-rubella group were seropositive for rubella. 6 weeks after vaccination, measles seroconversion in the measles-rubella plus LJEV group (496 [98%] of 507) was non-inferior to that in the measles-rubella group (499 [99%] of 506; difference -0·8% [90% CI -2·6 to 1·1]) and rubella seroconversion in the measles-rubella plus LJEV group (478 [94%] of 507) was non-inferior to that in the measles-rubella group (473 [94%] of 506 infants; difference 0·8% [90% CI -1·8 to 3·4]). There were no serious adverse events in either group and no evidence of a difference between the two groups in the prevalence of any local adverse event (redness, rashes, and pain) or systemic adverse event (fever, allergy, respiratory infections, diarrhoea, and vomiting). Fever was the most common adverse event (97 [19%] of 507 infants in the measles-rubella plus LJEV group; 108 [21%] of 506 infants in the measles-rubella group).

INTERPRETATION:
The evidence of similar seroconversion and safety with co-administered LJEV and measles-rubella vaccines supports the co-administration of these vaccines to infants aged 8 months. These results will be important for measles and rubella elimination and the expansion of Japanese encephalitis vaccination in countries where it is endemic.

Photochem Photobiol. 2019 Jan;95(1):446-452. doi: 10.1111/php.13004. Epub 2018 Oct 3.

Effect of A Sun Protection Intervention on the Immune Response to Measles Booster Vaccination in Infants in Rural South Africa.

Wright CY, Lucas RM, D'Este C, Kapwata T, Kunene Z, Swaminathan A, Mathee A, Albers PN.
South Africa, Australia

Abstract

The incidence of many serious childhood infections can be reduced by vaccination. High sun exposure at the time of vaccination has been associated with a reduced antigen-specific immune response. We hypothesized that providing sun protection advice and equipment to mothers of children who were waiting to be vaccinated would result in a more robust immunization response. **We conducted a pilot study in 2015/2016 (data analyzed in 2017-2018) among 98 Black African children (~18 months of age) receiving the booster measles vaccination at two clinics in South Africa. Clinics were randomized to receive (or not) sun protection advice and equipment.** We recorded demographic information on children and mothers and data on the child's usual sun exposure. At approximately 4 weeks' postmeasles vaccination, we measured measles immunoglobulin G levels in children. All children with blood results (n = 87, 89%) across both groups had antibody titers higher than 200 mIU mL which was considered the protective antibody concentration. **There was no statistically significant difference in titers between groups: geometric difference in mean titers 1.13 mIU mL (95% CI 0.85, 1.51; P = 0.39) and 1.38 mIU mL (95% CI 0.90, 2.11, P = 0.14) for unadjusted and adjusted analyses, respectively.** This study demonstrated that a sun protection intervention study could be performed in a developing-world pediatric vaccination setting. Although the sun protection intervention around the time of vaccination was not associated with a higher antibody level, given the potential importance of such an effect, a larger study should be considered.

Measles, mumps, rubella (MMR) vaccine

Meningococcal vaccine

Vaccine. 2018 Nov 29;36(50):7609-7617. doi: 10.1016/j.vaccine.2018.10.096. Epub 2018 Nov 7. (Open access available)

Immunogenicity and safety of the 4CMenB and MenACWY-CRM meningococcal vaccines administered concomitantly in infants: A phase 3b, randomized controlled trial.

Macias Parra M, Gentile A, Vazquez Narvaez JA, Capdevila A, Minguez A, Carrascal M, Willemsen A, Bhusal C, Toneatto D.
Mexico, Argentina, The Netherlands, Italy

BACKGROUND:
Invasive meningococcal disease has its highest incidence in infants. Co-administration of serogroup B (4CMenB) and quadrivalent conjugate (MenACWY-CRM) vaccines could protect against 5 clinically-relevant meningococcal serogroups.
METHODS:
This phase 3b, open, multicenter study (NCT02106390), conducted in Mexico and Argentina, enrolled and randomized (1:1:1) 750 healthy infants to receive either 4CMenB co-administered with MenACWY-CRM (4CMenB/MenACWY group), 4CMenB (4CMenB group), or MenACWY-CRM alone (MenACWY group) at ages 3, 5, 7 and 13 months. Non-inferiority of

immune responses of co-administration to single administration of vaccines was assessed at 1 month post-booster dose (primary objective). Immunogenicity was evaluated pre- and 1 month post-primary and booster vaccinations using human serum bactericidal assay (hSBA). Safety was assessed.

RESULTS:
At 1 month post-booster vaccination, between-group hSBA geometric mean titer (GMT) ratios ranged from 0.89 to 1.03 for serogroup B strains (group 4CMenB/MenACWY over 4CMenB), and from 1.05 to 2.48 for ACWY serogroups (group 4CMenB/MenACWY over MenACWY). The lower limit of the 2-sided 95% confidence intervals for all GMT ratios was >0.5; the primary objective was demonstrated. Across all groups and serogroup B strains, 68-100% and 87-100% of children had hSBA titers ≥5 at 1 month post-primary and booster vaccination, respectively. For serogroups ACWY, ≥96% (post-primary vaccination) and ≥98% (post-booster vaccination) of children in all groups had hSBA titers ≥4. Post-booster vaccination, GMTs increased ≥5.99-fold from pre-booster values for each strain/serogroup. Solicited adverse events (AEs) were more frequent in groups 4CMenB/MenACWY and 4CMenB than in MenACWY; incidence of all other AEs was similar between groups. Serious AEs were reported for 6, 13, and 11 participants in groups 4CMenB/MenACWY, 4CMenB, and MenACWY, respectively; 1 (group 4CMenB) was considered vaccine-related.

CONCLUSION:
Immune responses elicited by co-administration of 4CMenB and MenACWY-CRM was non-inferior to single immunization. Co-administration of vaccines was immunogenic and well tolerated in infants. ClinicalTrials.gov: NCT02106390.

Pneumococcal vaccine

Clin Infect Dis. 2018 Sep 3. doi: 10.1093/cid/ciy743. [Epub ahead of print] (Open access available)

Safety and immunogenicity of pneumococcal conjugate vaccines in a high-risk population: a randomised controlled trial of 10-valent and 13-valent PCV in Papua New Guinean infants.

Pomat WS, van den Biggelaar AHJ, Wana S, Greenhill AR, Ford R, Orami T, Passey M, Jacoby P, Kirkham LA, Lehmann D, Richmond PC; 10v13v PCV trial team.
Papua New Guinea, Australia.

Background:
There are little data on the immunogenicity of PCV10 and PCV13 in the same high-risk population.

Methods:

PCV10 and PCV13 were studied head-to-head in a randomized controlled trial in Papua New Guinea in which **262 infants received three doses of PCV10 or PCV13 at 1, 2, and 3 months of age.** Serotype-specific IgG concentrations, and pneumococcal and non-typeable Haemophilus influenzae (NTHi) carriage were assessed pre-vaccination, and at 4 and 9 months of age. Infants were followed for safety until 9 months of age.

Results:
One month after the third dose of PCV10 or PCV13, >80% of infants had IgG concentrations ≥0·35µg/mL for vaccine serotypes, and six months post-vaccination IgG concentrations ≥0·35µg/mL were maintained for 8/10 shared PCV serotypes in >75% of children vaccinated with either PCV10 or PCV13. Children carried a total of 65 different pneumococcal serotypes (plus nonserotypeable). At 4 months of age, 92% (95% confidence interval (CI) 85-96) of children vaccinated with PCV10 and 81% (95% 72-88) vaccinated with PCV13 were pneumococcal carriers (p = 0·023), while no differences were seen at 9 months of age, or for NTHi carriage. Both vaccines were well tolerated and not associated with serious adverse events.

Conclusions:
Infant vaccination with 3 doses of PCV10 or PCV13 is safe and immunogenic in a highly endemic setting; however, to significantly reduce pneumococcal disease in these settings, PCVs with broader serotype coverage and potency to reduce pneumococcal carriage are needed.

Vaccines (Basel). 2019 Feb 4;7(1). pii: E17. doi: 10.3390/vaccines7010017. (Open access available)

Immunogenicity and Immune Memory after a Pneumococcal Polysaccharide Vaccine Booster in a High-Risk Population Primed with 10-Valent or 13-Valent Pneumococcal Conjugate Vaccine: A Randomized Controlled Trial in Papua New Guinean Children.

van den Biggelaar AHJ, Pomat WS, Masiria G, Wana S, Nivio B, Francis J, Ford R, Passey M, Kirkham LA, Jacoby P, Lehmann D, Richmond P; 10v13v PCV Trial Team.
Australia, Papua New Guinea

Abstract
We investigated the immunogenicity, seroprotection rates and persistence of immune memory in young children at high risk of pneumococcal disease in Papua New Guinea (PNG). **Children were primed with 10-valent (PCV10) or 13-valent pneumococcal conjugate vaccines (PCV13) at 1, 2 and 3 months of age and randomized at 9 months to receive PPV (PCV10/PPV-vaccinated, n = 51; PCV13/PPV-vaccinated, n = 52) or no PPV** (PCV10/PPV-naive, n = 57; PCV13/PPV-naive, n = 48). **All children received a micro-dose of PPV at 23 months of age to study the capacity to respond to a pneumococcal challenge. PPV vaccination resulted in significantly increased IgG responses** (1.4 to 10.5-fold change) at 10 months of age for all PPV-serotypes tested. Both PPV-vaccinated and PPV-naive children responded to the 23-month challenge and post-challenge seroprotection rates (IgG ≥ 0.35

µg/mL) were similar in the two groups (80⁻100% for 12 of 14 tested vaccine serotypes). **These findings show that PPV is immunogenic in 9-month-old children at high risk of pneumococcal infections and does not affect the capacity to produce protective immune responses.** Priming with currently available PCVs followed by a PPV booster in later infancy could offer improved protection to young children at high risk of severe pneumococcal infections caused by a broad range of serotypes.

Polio vaccine

Vaccine. 2018 Oct 29;36(45):6782-6789. doi: 10.1016/j.vaccine.2018.09.023. Epub 2018 Sep 21.

Safety and immunogenicity of inactivated poliovirus vaccine made from Sabin strains: A phase II, randomized, dose-finding trial.

Chu K, Ying Z, Wang L, Hu Y, Xia J, Chen L, Wang J, Li C, Zhang Q, Gao Q, Hu Y.
China

BACKGROUND:
In order to completely eradicate polio caused by wild poliovirus infection as well as vaccine-associated paralytic polio (VAPP), Sabin inactivated poliovirus vaccine (sIPV) should be developed to meet the requirements for biosafety and affordable strategy in the developing countries.

METHOD:
A randomized, double-blinded clinical trial was conducted to compare the immunogenicity and safety among infants aged 2 months (60-90 days) receiving five different vaccination regimens: the test groups (A, B, and C) received three doses of sIPV with high, medium, and low D antigen content, respectively, on the month 0, 1, 2 schedule; two control groups (D and E) received three doses of conventional IPV (cIPV) or sIPV (CAMS), respectively, on the same schedule as that of test groups. Serum samples were collected immediately before the 1st dose and 30 days after the 3rd dose vaccination to assess the immunogenicity. Adverse events occurring within 30 days after each dose were collected to assess the safety.

RESULTS:
After three doses, seroconversion rates in groups A-E were 100%, 98.2%, 100%, 100%, and 100%, respectively, for type 1; 99.1%, 100%, 98.1%, 100%, and 97.1%, respectively, for type 2; and 100%, 100%, 100%, 100%, and 99.0%, respectively, for type 3. The seropositive rates (≥1:8) of groups A-E for all types were nearly 100%. The GMTs in the target dose group (group B) were 4635, 342, and 2218 for type 1-3, respectively. The most common injection-site and systemic adverse reactions were swelling and fever respectively. The swelling (4.2%, P = 0.0075) and fever (58.3%, P = 0.0188) frequency of group A were statistically significantly higher than any other groups.

CONCLUSION:

The test sIPV generally demonstrated good safety and immunogenicity. The medium-D antigen dose would be a preferred choice for the further phase III clinical trial in consideration of its high immunogenicity for all serotypes and the satisfying tolerance.

Rotavirus vaccine

Cochrane Database Syst Rev. 2019 Mar 25;3:CD008521. doi: 10.1002/14651858.CD008521.pub4. (Open access available)

Vaccines for preventing rotavirus diarrhoea: vaccines in use.

Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N.

Abstract
BACKGROUND:
Rotavirus results in more diarrhoea-related deaths in children under five years than any other single agent in countries with high childhood mortality. It is also a common cause of diarrhoea-related hospital admissions in countries with low childhood mortality. Rotavirus vaccines that have been prequalified by the World Health Organization (WHO) include a monovalent vaccine (RV1; Rotarix, GlaxoSmithKline), a pentavalent vaccine (RV5; RotaTeq, Merck), and, more recently, another monovalent vaccine (Rotavac, Bharat Biotech).

OBJECTIVES:
To evaluate rotavirus vaccines prequalified by the WHO (RV1, RV5, and Rotavac) for their efficacy and safety in children.

SEARCH METHODS:
On 4 April 2018 we searched MEDLINE (via PubMed), the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (published in the Cochrane Library), Embase, LILACS, and BIOSIS. 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) in children comparing rotavirus vaccines prequalified for use by the WHO versus placebo or no intervention.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed trial eligibility and assessed risks of bias. One review 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 analysis by country mortality rate and used GRADE to evaluate evidence certainty.

MAIN RESULTS:

Fifty-five trials met the inclusion criteria and enrolled a total of 216,480 participants. Thirty-six trials (119,114 participants) assessed RV1, 15 trials (88,934 participants) RV5, and four trials (8432 participants) Rotavac. RV1 Children vaccinated and followed up the first year of life In low-mortality countries, RV1 prevents 84% of severe rotavirus diarrhoea cases (RR 0.16, 95% CI 0.09 to 0.26; 43,779 participants, 7 trials; high-certainty evidence), and probably prevents 41% of cases of severe all-cause diarrhoea (RR 0.59, 95% CI 0.47 to 0.74; 28,051 participants, 3 trials; moderate-certainty evidence). **In high-mortality countries, RV1 prevents 63% of severe rotavirus diarrhoea cases (RR 0.37, 95% CI 0.23 to 0.60; 6114 participants, 3 trials; high-certainty evidence), and 27% of severe all-cause diarrhoea cases (RR 0.73, 95% CI 0.56 to 0.95; 5639 participants, 2 trials; high-certainty evidence).** Children vaccinated and followed up for two years. **In low-mortality countries, RV1 prevents 82% of severe rotavirus diarrhoea cases (RR 0.18, 95% CI 0.14 to 0.23; 36,002 participants, 9 trials; high-certainty evidence), and probably prevents 37% of severe all-cause diarrhoea episodes (rate ratio 0.63, 95% CI 0.56 to 0.71; 39,091 participants, 2 trials; moderate-certainty evidence). In high-mortality countries RV1 probably prevents 35% of severe rotavirus diarrhoea cases (RR 0.65, 95% CI 0.51 to 0.83; 13,768 participants, 2 trials; high-certainty evidence), and 17% of severe all-cause diarrhoea cases** (RR 0.83, 95% CI 0.72 to 0.96; 2764 participants, 1 trial; moderate-certainty evidence).No increased risk of serious adverse events (SAE) was detected (RR 0.88 95% CI 0.83 to 0.93; high-certainty evidence). There were 30 cases of intussusception reported in 53,032 children after RV1 vaccination and 28 cases in 44,214 children after placebo or no intervention (RR 0.70, 95% CI 0.46 to 1.05; low-certainty evidence).RV5 Children vaccinated and followed up the first year of life In low-mortality countries, RV5 probably prevents 92% of severe rotavirus diarrhoea cases (RR 0.08, 95% CI 0.03 to 0.22; 4132 participants, 5 trials; moderate-certainty evidence). We did not identify studies reporting on severe all-cause diarrhoea in low-mortality countries. **In high-mortality countries, RV5 prevents 57% of severe rotavirus diarrhoea (RR 0.43, 95% CI 0.29 to 0.62; 5916 participants, 2 trials; high-certainty evidence), but there is probably little or no difference between vaccine and placebo for severe all-cause diarrhoea (RR 0.80, 95% CI 0.58 to 1.11**; 1 trial, 4085 participants; moderate-certainty evidence).Children vaccinated and followed up for two years. In low-mortality countries, RV5 prevents 82% of severe rotavirus diarrhoea cases (RR 0.18, 95% CI 0.08 to 0.39; 7318 participants, 4 trials; moderate-certainty evidence). We did not identify studies reporting on severe all-cause diarrhoea in low-mortality countries. In high-mortality countries, RV5 prevents 41% of severe rotavirus diarrhoea cases (RR 0.59, 95% CI 0.43 to 0.82; 5885 participants, 2 trials; high-certainty evidence), and 15% of severe all-cause diarrhoea cases (RR 0.85, 95% CI 0.75 to 0.98; 5977 participants, 2 trials; high-certainty evidence).No increased risk of serious adverse events (SAE) was detected (RR 0.93 95% CI 0.86 to 1.01; moderate to high-certainty evidence). There were 16 cases of intussusception in 43,629 childrenafter RV5 vaccination and 20 cases in 41,866 children after placebo (RR 0.77, 95% CI 0.41 to 1.45; low-certainty evidence).Rotavac Children vaccinated and followed up the first year of life Rotavac has not been assessed in any RCT
in countries with low child mortality. In India, a high-mortality country, Rotavac probably prevents 57% of severe rotavirus diarrhoea cases (RR 0.43, 95% CI 0.30 to 0.60; 6799 participants, moderate-certainty evidence); the trial did not report on severe all-cause diarrhoea at one-year follow-up.Children vaccinated and followed up for two yearsRotavac probably prevents 54% of severe rotavirus diarrhoea cases in India (RR 0.46, 95% CI 0.35 to 0.60; 6541 participants, 1 trial; moderate-certainty evidence), and 16% of severe all-cause

diarrhoea cases (RR 0.84, 95% CI 0.71 to 0.98; 6799 participants, 1 trial; moderate-certainty evidence).No increased risk of serious adverse events (SAE) was detected (RR 0.93 95% CI 0.85 to 1.02; moderate-certainty evidence). There were eight cases of intussusception in 5764 children after Rotavac vaccination and three cases in 2818 children after placebo (RR 1.33, 95% CI 0.35 to 5.02; very low-certainty evidence).There was insufficient evidence of an effect on mortality from any rotavirus vaccine (198,381 participants, 44 trials; low- to very low-certainty evidence), as the trials were not powered to detect an effect at this endpoint.

AUTHORS' CONCLUSIONS:
RV1, RV5, and Rotavac prevent episodes of rotavirus diarrhoea. Whilst the relative effect estimate is smaller in high-mortality than in low-mortality countries, there is a greater number of episodes prevented in these settings as the baseline risk is much higher. We found no increased risk of serious adverse events.

Vaccine. 2018 Sep 18;36(39):5872-5878. doi: 10.1016/j.vaccine.2018.08.027. Epub 2018 Aug 23. (Open access available)

Molecular characterisation of rotavirus strains detected during a clinical trial of the human neonatal rotavirus vaccine (RV3-BB) in Indonesia.

Cowley D, Nirwati H, Donato CM, Bogdanovic-Sakran N, Boniface K, Kirkwood CD, Bines JE. Australia, Indonesia

BACKGROUND:
The RV3-BB human neonatal rotavirus vaccine aims to provide protection from severe rotavirus disease from birth. The aim of the current study was to characterise the rotavirus strains causing gastroenteritis during the Indonesian Phase IIb efficacy trial.

METHODS:
A randomized, double-blind placebo-controlled trial involving 1649 participants was conducted from January 2013 to July 2016 in Central Java and Yogyakarta, Indonesia. Participants received three doses of oral RV3-BB vaccine with the first dose given at 0-5 days after birth (neonatal schedule), or the first dose given at ~8 weeks after birth (infant schedule), or placebo (placebo schedule). Stool samples from episodes of gastroenteritis were tested for rotavirus using EIA testing, positive samples were genotyped by RT-PCR. Full genome sequencing was performed on two representative rotavirus strains.

RESULTS:
There were 1110 episodes of acute gastroenteritis of any severity, 105 episodes were confirmed as rotavirus gastroenteritis by EIA testing. **The most common genotype identified was G3P[8] (90/105), the majority (52/56) of severe (Vesikari score ≥11) rotavirus gastroenteritis episodes were due to the G3P[8] strain.** Full genome analysis of two representative G3P[8] samples demonstrated the strain was an inter-genogroup reassortant, containing an equine-like G3 VP7, P[8] VP4 and a genogroup 2 backbone I2-R2-

C2-M2-A2-N2-T2-E2-H2. The complete genome of the Indonesian equine-like G3P[8] strain demonstrated highest genetic identity to G3P[8] strains circulating in Hungary and Spain.

CONCLUSIONS:
The dominant circulating strain during the Indonesian Phase IIb efficacy trial of the RV3-BB vaccine was an equine-like G3P[8] strain. The equine-like G3P[8] strain is an emerging cause of severe gastroenteritis in Indonesia and in other regions.

Vaccine. 2018 Sep 5;36(37):5519-5523. doi: 10.1016/j.vaccine.2018.07.064. Epub 2018 Aug 10. (Open access available)

Non-interference of Bovine-Human reassortant pentavalent rotavirus vaccine ROTASIIL® with the immunogenicity of infant vaccines in comparison with a licensed rotavirus vaccine.

Desai S, Rathi N, Kawade A, Venkatramanan P, Kundu R, Lalwani SK, Dubey AP, Venkateswara Rao J, Narayanappa D, Ghildiyal R, Gogtay NJ, Venugopal P, Palkar S, Munshi R, Bavdekar A, Juvekar S, Ganguly N, Niyogi P, Uttam KG, Kondekar A, Kumbhar D, Mohanlal S, Agarwal MC, Shetty P, Antony K, Gunale B, Dharmadhikari A, Deshpande J, Nalavade U, Sharma D, Bansal A, Tang Y, Flores J, Kulkarni PS.
India, USA

BACKGROUND:
A newly developed bovine-human reassortant pentavalent vaccine (BRV-PV, ROTASIIL®) was tested for its potential effect on the immunogenicity of concomitantly administered EPI vaccines in infants in a randomized controlled study in India.

METHODS:
In this Phase III, multicenter, open label, randomized, controlled study, three doses of BRV-PV or two doses of Rotarix® and one dose of placebo were given to healthy infants at 6, 10, and 14 weeks of age. Subjects also received three doses of DTwP-HepB-Hib (diphtheria, tetanus, whole-cell pertussis, hepatitis B, and haemophilus influenzae type b conjugate - pentavalent vaccine) and oral polio vaccine concomitantly at 6, 10, and 14 weeks of age and a single dose of inactivated polio vaccine at 14 weeks of age. Blood samples were collected four weeks after the final vaccination to assess immune responses to all the vaccines administered. For diphtheria, tetanus, hepatitis B, Hib, polio type 1, and polio type 3 antibodies, non-interference was to be supported if the lower limit of the two-sided 90% confidence interval (CI) for the seroprotection rate difference for the BRV-PV group minus the Rotarix® group was >10.0%. For pertussis antibodies, non-interference was to be supported if the lower limit of the two-sided 90% CI for the ratio of geometric mean concentrations (GMCs) was >0.5.

RESULTS:
A total of 1500 infants were randomized to either BRV-PV (1125 infants) or Rotarix® (375 infants), of which 1341 completed the study as per the protocol. More than 97% of subjects achieved seroprotective antibody titres against diphtheria, tetanus, hepatitis B, Hib, polio

type 1, and polio type 3 in both groups. The difference in seroprotection rates between the BRV-PV group and the Rotarix® group for all these antibodies was less than 1%. The ratio of GMCs of anti-pertussis IgG concentrations for the BRV-PV group versus Rotarix® was 1.04 [90% CI: 0.90; 1.19].
CONCLUSION:
BRV-PV does not interfere with the immunogenicity of concomitantly administered routine infants vaccines.

Cell Host Microbe. 2018 Aug 8;24(2):197-207.e4. doi: 10.1016/j.chom.2018.07.005.

Effect of Antibiotic-Mediated Microbiome Modulation on Rotavirus Vaccine Immunogenicity: A Human, Randomized-Control Proof-of-Concept Trial.

Harris VC, Haak BW, Handley SA, Jiang B, Velasquez DE, Hykes BL Jr, Droit L, Berbers GAM, Kemper EM, van Leeuwen EMM, Boele van Hensbroek M, Wiersinga WJ.
The Netherlands, USA

Abstract
Rotavirus vaccines (RVV) protect against childhood gastroenteritis caused by rotavirus (RV) but have decreased effectiveness in low- and middle-income settings. **This proof-of-concept, randomized-controlled, open-label trial tested if microbiome modulation can improve RVV immunogenicity.** Healthy adults were randomized and administered broad-spectrum (oral vancomycin, ciprofloxacin, metronidazole), narrow-spectrum (vancomycin), or no antibiotics and then vaccinated with RVV, 21 per group per protocol. Baseline anti-RV IgA was high in all subjects. Although antibiotics did not alter absolute anti-RV IgA titers, RVV immunogenicity was boosted at 7 days in the narrow-spectrum group. Further, antibiotics increased fecal shedding of RV while also rapidly altering gut bacterial beta diversity. Beta diversity associated with RVV immunogenicity boosting at day 7 and specific bacterial taxa that distinguish RVV boosters and RV shedders were identified. Despite the negative primary endpoint, this study demonstrates that microbiota modification alters the immune response to RVV and supports further exploration of microbiome manipulation to improve RVV immunogenicity.

Clin Infect Dis. 2019 Feb 16. pii: ciz140. doi: 10.1093/cid/ciz140. [Epub ahead of print] (Open access available)

The impact of improved water, sanitation and hygiene on oral rotavirus vaccine immunogenicity in Zimbabwean infants: sub-study of a cluster-randomized trial.

Church JA, Rukobo S, Govha M, Lee B, Carmolli MP, Chasekwa B, Ntozini R, Mutasa K, McNeal MM, Majo FD, Tavengwa NV, Moulton LH, Humphrey JH, Kirkpatrick BD, Prendergast AJ.
Zimbabwe

BACKGROUND:

Oral vaccines have lower efficacy in developing compared
to developed countries. Poor water, sanitation and hygiene (WASH) may contribute to reduced oral vaccine immunogenicity.

METHODS:
We conducted a cluster-randomized 2x2 factorial trial in rural Zimbabwe (NCT01824940). Pregnant women and their infants were eligible if they lived in clusters randomized to: 1) Standard-of-care (52 clusters); 2) Improved infant feeding (53 clusters); 3) WASH: ventilated improved pit latrine, two hand-washing stations, liquid soap, chlorine, infant play space, hygiene counseling (53 clusters); or 4) Feeding+WASH (53 clusters). **This sub-study compared oral rotavirus vaccine seroconversion (primary outcome), and seropositivity and geometric mean titre (GMT) (secondary outcomes), in WASH versus non-WASH infants by intention-to-treat analysis.**

RESULTS:
We included 801 infants with documented rotavirus vaccine receipt and post-vaccine titre measurements (329 from 84 WASH clusters; 472 from 102 non-WASH clusters);
328 infants with pre-vaccination titres were included in the primary outcome. 33/109 (30.3%) infants in the WASH group seroconverted following rotavirus vaccination, compared to 43/219 (19.6%) in the non-WASH group (absolute difference 10.6% (95%CI 0.54, 20.7); p=0.031). In the WASH versus non-WASH groups, 90/329 (27.4%) versus 107/472 (22.7%) were seropositive post-vaccination (absolute difference 4.7% (95%CI -1.4, 10.8; p=0.130) and anti-rotavirus GMT was 18.4U/mL (95% CI 15.6, 21.7) versus 14.9U/mL (95% CI 13.2, 16.8); p=0.072. **After restricting analyses to infants who received both doses of rotavirus vaccine, the effect of WASH on seroconversion was greater (absolute difference 13.7% (95%CI 2.0, 25.4); p=0.016).**

CONCLUSIONS:
Improvements in household WASH led to modest but significant increases in seroconversion to oral rotavirus vaccine in rural Zimbabwean infants.

Epidemiology. 2018 Nov;29(6):867-875. doi: 10.1097/EDE.0000000000000909. (Open access available)

Timing of Rotavirus Vaccine Doses and Severe Rotavirus Gastroenteritis Among Vaccinated Infants in Low- and Middle-income Countries.

Gruber JF, Becker-Dreps S, Hudgens MG, Brookhart MA, Thomas JC, Jonsson Funk M.
USA

BACKGROUND:
Altering rotavirus vaccine schedules may improve vaccine performance in low- and middle-income countries. We analyzed data from clinical trials of the monovalent (RV1) and pentavalent (RV5) rotavirus vaccines in low- and middle-income countries to understand the association between vaccine dose timing and severe rotavirus gastroenteritis incidence.

METHODS:
We assessed the association between variations in rotavirus vaccine administration schedules and severe rotavirus gastroenteritis risk. We used the complement of the Kaplan-Meier survival estimator to estimate risk differences for different schedules. To adjust risk differences (RDs) for confounding, we calibrated estimates in the vaccinated arm using estimates from the placebo arm.

RESULTS:
There were 3,114 and 7,341 children included from the RV1 and RV5 trials, respectively. The 18-month adjusted severe rotavirus gastroenteritis risk was 4.0% (95% confidence interval [CI] = 1.1, 7.1) higher for those receiving their first RV5 dose at <6 versus ≥6 weeks. For RV1, there was a 4.0% (95% CI = 0.0, 8.2) increase in 12-month adjusted risk for a 4- versus 6-week interval between doses. Further analysis revealed those receiving their first RV5 dose at 3-4 and 5-7 weeks had 2.9% (95% CI = 0.8, 5.3) and 1.3% (95% CI = -0.3, 3.0), respectively, higher risk compared with those at 9-12 weeks. Those receiving their first dose at 8 weeks had the lowest risk (RD: -2.6% [95% CI = -5.4, -0.1]) compared with those at 9-12 weeks.

CONCLUSIONS:
A modest delay in rotavirus vaccination start and increase in interval between doses may be associated with lower severe rotavirus gastroenteritis risk in low- and middle-income countries.

Salmonella typhi vaccine

Schistosomiasis vaccine

PLoS Negl Trop Dis. 2018 Dec 7;12(12):e0006968. doi: 10.1371/journal.pntd.0006968. eCollection 2018 Dec. (Open access available)

Safety and efficacy of the rSh28GST urinary schistosomiasis vaccine: A phase 3 randomized, controlled trial in Senegalese children.

Riveau G, Schacht AM, Dompnier JP, Deplanque D, Seck M, Waucquier N, Senghor S, Delcroix-Genete D, Hermann E, Idris-Khodja N, Levy-Marchal C, Capron M, Capron A.
Senegal, France

BACKGROUND:
Urinary schistosomiasis, the result of infection by Schistosoma haematobium (Sh), remains a major global health concern. A schistosome vaccine could represent a breakthrough in schistosomiasis control strategies, which are presently based on treatment with praziquantel (PZQ). We report the safety and efficacy of the vaccine candidate recombinant 28-kDa glutathione S-transferase of Sh (rSh28GST) designated as Bilhvax, in a phase 3 trial conducted in Senegal.

METHODS AND FINDINGS:
After clearance of their ongoing schistosomiasis infection with two doses of PZQ, 250 children aged 6-9 years were randomized to receive three subcutaneous injections of either rSh28GST/Alhydrogel (Bilhvax group) or Alhydrogel alone (control group) at week 0 (W0), W4, and W8 and then a booster at W52 (one year after the first injection). PZQ treatment was given at W44, according to previous phase 2 results. The primary endpoint of the analysis was efficacy, evaluated as a delay of recurrence of urinary schistosomiasis, defined by a microhematuria associated with at least one living Sh egg in urine from baseline to W152. During the 152-week follow-up period, there was no difference between study arms in the incidence of serious adverse events. The median follow-up time for subjects without recurrence was 22.9 months for the Bilhvax group and 18.8 months for the control group (log-rank p = 0.27). At W152, 108 children had experienced at least one recurrence in the Bilhvax group versus 112 in the control group. Specific immunoglobulin (Ig)G1, IgG2, and IgG4, but not IgG3 or IgA titers, were increased in the vaccine group.

CONCLUSIONS:
While Bilhvax was immunogenic and well tolerated by infected children, a sufficient efficacy was not reached. The lack of effect may be the result of several factors, including interference by individual PZQ treatments administered each time a child was found infected, or the chosen vaccine-injection regimen favoring blocking IgG4 rather than protective IgG3 antibodies. These observations contrasting with results obtained in experimental models will help in the design of future trials.

Tuberculosis vaccine

(also see Tuberculosis, Isoniazid preventative therapy)

Typhoid vaccine

Varicella vaccine

Vitamin A

Arch Dis Child. 2019 Mar;104(3):217-226. doi: 10.1136/archdischild-2018-315242. Epub 2018 Nov 13. (Open access available)

Early neonatal vitamin A supplementation and infant mortality: an individual participant data meta-analysis of randomised controlled trials.

West KP, Wu LS, Ali H, Klemm RDW, Edmond KM, Hurt L, Kirkwood B, Newton S, Shannon C, Taneja S, Mazumder S, Bhatia K, Bhandari N, Katz J, Tielsch JM, Humphrey J, Agoestina T, Soofi SB, Ariff S, Bhatti Z, Cousens S, Bhutta ZA, Ntozini R, Masanja H, Smith ER, Muhihi A, Fawzi W, Bahl R, Martines J, Yoshida S.
Author information

USA, Bangladesh, Australia, UK, Ghana, USA, India, Indonesia, Pakistan, Zimbabwe, Tanzania, World Health Organization, Switzerland, Norway

BACKGROUND:
Biannual vitamin A supplementation is a well-established survival tool for preschool children 6 months and older in vitamin A deficient populations but this schedule misses the opportunity to intervene on most young infant deaths. Randomised trials of neonatal vitamin A supplementation (NVAS) in the first few days of life to assess its impact on under 6-month mortality in low/middle-income countries have had varying results.

METHODS:
Investigators of 11 published randomised placebo-controlled NVAS trials (n=163 567 children) reanalysed their data according to an agreed plan and pooled the primary outcomes of mortality from supplementation through 6 and 12 months of age using random effects models and meta-regression. One investigator withdrew but allowed use of the data.

FINDINGS:
Overall there was no effect of NVAS on infant survival through 6 (risk ratio (RR) 0.97; 95% CI 0.89 to 1.06) or 12 months of age (RR 1.00; 95% CI 0.93 to 1.08) but results varied by study population characteristics. NVAS significantly reduced 6-month mortality among the trials conducted in Southern Asia (RR 0.87; 95% CI 0.77 to 0.98), in contexts with moderate or severe vitamin A deficiency (defined as 10% or higher proportion of women with serum retinol <0.7 µmol/L or 5% or more women with night blindness) (RR 0.87; 95% CI 0.80 to 0.94), early infant mortality was 30 or more per 1000 live births (RR 0.91; 95% CI 0.85 to 0.98), 75% or more of infant mortality occurred in the first 6 months of life (RR 0.92; 95% CI 0.84 to 1.01), or where >32% mothers had no schooling (RR 0.88; 95% CI 0.80 to 0.96). NVAS did not reduce mortality in the first 6 months of life in trials conducted in Africa, in contexts characterised by a low prevalence of vitamin A deficiency, lower rates of infant mortality and where maternal education was more prevalent. There was a suggestion of increased infant mortality in trials conducted in Africa (RR 1.07; 95% CI 1.00 to 1.15). Individual-level characteristics such as sex, birth weight, gestational age and size, age at dosing, parity, time of breast feeding initiation, maternal education and maternal vitamin A supplementation did not modify the impact of NVAS.

CONCLUSION:
NVAS reduced infant mortality in South Asia, in contexts where the prevalence of maternal vitamin A deficiency is moderate to severe and early infant mortality is high; but it had no beneficial effect on infant survival in Africa, in contexts where the prevalence of maternal vitamin A deficiency is lower, early infant mortality is low.

*** Eur J Pediatr. 2019 Jun 17. doi: 10.1007/s00431-019-03412-w.

Oral vitamin A supplementation in very low birth weight neonates: a randomized controlled trial.

Basu S, Khanna P, Srivastava R, Kumar A

India

Abstract
This randomized double-blind placebo-controlled trial evaluated the effects of early postnatal oral vitamin A supplementation (VAS) in 196 inborn very-low birth weight (VLBW) infants requiring respiratory support at 24 h of age. Eligible infants were randomized to receive aqueous syrup of vitamin A (10,000 IU of retinol/dose; n = 98) or placebo (n = 98) on alternate days for 28 days. **Primary outcome variable was composite incidence of all-cause mortality and/or oxygen requirement for 28 days**. Secondary outcome variables were safety/tolerability of VAS, serum retinol concentration at recruitment and day 28, duration of oxygen requirement and respiratory support and incidences of complications. **On intention-to-treat analysis, composite incidence of all-cause mortality and oxygen requirement for 28 days was significantly lower in vitamin A group (relative risk (95% confidence interval), 0.440 (0.229-0.844); p < 0.05, number needed to benefit, 7).** Requirement and duration of oxygen supplementation and non-invasive respiratory support, incidences of late-onset sepsis, patent ductus arteriosus, and duration of hospital stay were also significantly lower in vitamin A group. Serum retinol concentration improved significantly after VAS. No major adverse effect was observed.Conclusions: **Early postnatal oral VAS was associated with better composite outcome of all-cause mortality and oxygen requirement without any major adverse effects**.

Trans R Soc Trop Med Hyg. 2019 Mar 1;113(3):110-115. doi: 10.1093/trstmh/try126. (Open access available)

Neonatal vitamin A supplementation and immune responses to oral polio vaccine in Zimbabwean infants.

Church JA, Rukobo S, Govha M, Carmolli MP, Diehl SA, Chasekwa B, Ntozini R, Mutasa K, Humphrey JH, Kirkpatrick BD, Prendergast AJ.
Author information
Zimbabwe, UK, USA

BACKGROUND:
Micronutrient deficiencies may contribute to reduced oral vaccine immunogenicity in developing countries. We hypothesised that neonatal vitamin A supplementation (NVAS) would improve oral vaccine responses.

METHODS:
We performed a cross-sectional study of infants recruited at birth to the Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO) trial, a randomised controlled trial of single, high-dose NVAS vs placebo conducted in Zimbabwe between 1997-2001. We measured poliovirus-specific IgA to type 1-3 polio strains by semiquantitative capture ELISA in cryopreserved plasma samples collected at 6 months of age.

RESULTS:

A total of 181 infants fulfilled inclusion criteria, of whom 80 were randomised to NVAS and 101 to placebo. There were no significant differences in baseline characteristics between groups. **At 6 months of age, median (IQR) vaccine titres for infants randomised to NVAS vs placebo were 932 (421-3001) vs 1774 (711-5431) for Sabin-1 (p=0.04); 1361 (705-3402) vs 2309 (1081-4283) for Sabin-2 (p=0.15); and 1584 (796-4216) vs 2260 (996-5723) for Sabin-3 (p=0.14), respectively**. After adjusting for breast feeding status, birth weight, season and infant sex in a linear regression model, there was only weak evidence of difference in log mean titres between vitamin A and placebo groups for Sabin-1 (p=0.08) and no evidence of difference in log mean titres for Sabin-2 and Sabin-3.

CONCLUSIONS:
NVAS did not augment oral polio vaccine responses in Zimbabwean infants. Further research is required to understand the impact of NVAS on responses to other oral vaccines.The trial is registered with clinicaltrials.gov identifier: NCT00198718.

Yale J Biol Med. 2018 Jun 28;91(2):83-94. eCollection 2018 Jun. (Open access available)

Improving Blood Retinol Concentrations with Complementary Foods Fortified with *Moringa oleifera* Leaf Powder - A Pilot Study.

Boateng L, Ashley I, Ohemeng A, Asante M, Steiner-Asiedu M.
Author information
Ghana

Abstract
Vitamin A deficiency (VAD) remains a major public health issue and is reported to be the cause of about 6 percent of child deaths under the age of 5 years in Africa. Inadequate dietary intake of vitamin A-rich foods is a major cause of VAD. *Moringa oleifera* leaf powder (MLP) is rich in nutrients particularly vitamin A and its use in infant feeding has been explored. This pilot study was designed to test the efficacy of MLP in improving blood retinol concentrations among infants in a rural district in Ghana. A subset of infants participating in a randomized controlled trial (ISRCTN14377902) were randomly assigned to receive one of the three study foods (*MCL-35g* and *MS-5g* both of which were fortified with MLP, and a third food, *CF-35g*, a cereal legume blend which served as the control food) in a feeding intervention that lasted for 6 weeks. Primary outcome of the pilot study was retinol levels measured in 5 ml of whole blood at baseline and endline using the iCheck™ Fluoro device. A total of 103 infant-mother pairs were recruited at baseline, of which 65 completed the study. All the infants in the study were vitamin A deficient at both baseline and endline when compared to the World Health Organization (WHO) threshold of 0.70µmol/l. There was however a marginal non-significant increase in blood vitamin A concentrations for all three groups at endline, with higher numerical increases seen in the two *Moringa* supplemented groups. VAD is a significant public health problem and MLP could be an affordable and sustainable means of combatting the issue. The efficacy of MLP in improving vitamin A status of infants however needs to be ascertained in well-designed trials involving larger numbers of infants and which will last for longer periods. Such studies will also be beneficial in helping

to establish the long-term acceptability of complementary foods that incorporate MLP in the target population.

Vitamin D

(See also Neonates – preterm and low birth weight)

Engl J Med. 2018 Aug 9;379(6):535-546. doi: 10.1056/NEJMoa1800927. (Open access available)

Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth.

Roth DE, Morris SK, Zlotkin S, Gernand AD, Ahmed T, Shanta SS, Papp E, Korsiak J, Shi J, Islam MM, Jahan I, Keya FK, Willan AR, Weksberg R, Mohsin M, Rahman QS, Shah PS, Murphy KE, Stimec J, Pell LG, Qamar H, Al Mahmud A.
Canada, USA, Bangladesh,

BACKGROUND:
It is unclear whether maternal vitamin D supplementation during pregnancy and lactation improves fetal and infant growth in regions where vitamin D deficiency is common.
METHODS:
We conducted a randomized, double-blind, placebo-controlled trial in Bangladesh to assess the effects of weekly prenatal vitamin D supplementation (from 17 to 24 weeks of gestation until birth) and postpartum vitamin D supplementation on the primary outcome of infants' length-for-age z scores at 1 year according to World Health Organization (WHO) child growth standards. One group received neither prenatal nor postpartum vitamin D (placebo group). Three groups received prenatal supplementation only, in doses of 4200 IU (prenatal 4200 group), 16,800 IU (prenatal 16,800 group), and 28,000 IU (prenatal 28,000 group). The fifth group received prenatal supplementation as well as 26 weeks of postpartum supplementation in the amount of 28,000 IU (prenatal and postpartum 28,000 group).
RESULTS:
Among 1164 infants assessed at 1 year of age (89.5% of 1300 pregnancies), there were no significant differences across groups in the mean (±SD) length-for-age z scores. Scores were as follows: placebo, -0.93±1.05; prenatal 4200, -1.11±1.12; prenatal 16,800, -0.97±0.97; prenatal 28,000, -1.06±1.07; and prenatal and postpartum 28,000, -0.94±1.00 (P=0.23 for a global test of differences across groups). Other anthropometric measures, birth outcomes, and morbidity did not differ significantly across groups. Vitamin D supplementation had expected effects on maternal and infant serum 25-hydroxyvitamin D and calcium concentrations, maternal urinary calcium excretion, and maternal parathyroid hormone concentrations. There were no significant differences in the frequencies of adverse events across groups, with the exception of a higher rate of possible hypercalciuria among the women receiving the highest dose.

CONCLUSIONS:

In a population with widespread prenatal vitamin D deficiency and fetal and infant growth restriction, maternal vitamin D supplementation from midpregnancy until birth or until 6 months post partum did not improve fetal or infant growth. (Funded by the Bill and Melinda Gates Foundation; ClinicalTrials.gov number, NCT01924013)

Indian Pediatr. 2018 Nov 15;55(11):951-956. (Open access available)

Supplementation with Three Different Daily Doses of Vitamin D3 in Healthy Pre-pubertal School Girls: A Cluster Randomized Trial.

Marwaha RK, Mithal A, Bhari N, Sethuraman G, Gupta S, Shukla M, Narang A, Chadda A, Gupta N, Sreenivas V, Ganie MA.
India

OBJECTIVE:
To compare the adequacy and efficacy of different doses of vitamin D3 in pre-pubertal girls.

DESIGN:
Cluster Randomized controlled trial.

SETTING:
Public school in Delhi, India, between August 2015 and February 2016.

PARTICIPANTS:
216 healthy pre-pubertal girls, aged 6.1-11.8 years.

INTERVENTION:
Daily supplementation with 600 IU (n=74), 1000 IU (n=67) or 2000 IU (n=75) of vitamin D3 under supervision for 6 months.

OUTCOME MEASURES:
Primary: Rise in serum 25 hydroxy Vitamin D (25(OH)D); Secondary: Change in bone formation and resorption markers.

RESULTS:
Following 6 months of supplementation, the mean (SD) rise in serum 25(OH)D was maximum with 2000 IU (24.09 (8.28) ng/mL), followed by with 1000 IU (17.96 (6.55) ng/mL) and 600 IU (15.48 (7.00) ng/mL). Serum 25(OH)D levels of ≥20 ng/mL were seen in 91% in 600 IU group , 97% in 1000 IU group and 100% in 2000 IU group. The overall mean (SD) rise in urinary calcium creatinine ratio (0.05 (0.28) to 0.13 (0.12) mg/mg), and serum procollagen type I N-terminal propeptide (538.9 (199.78) to 655.5 (218.24) ng/mL), and reduction in serum carboxy-terminal telopeptide (0.745 (0.23) to 0.382 (0.23) ng/mL) was significant (P<0.01). The change in the above parameters was comparable among the three groups after adjustment for age.

CONCLUSIONS:

Daily vitamin D supplementation with 600 IU to 2000 IU for 6 months results in Vitamin D sufficiency in >90% of pre-pubertal girls.

Nutrition. 2019 Jan;57:63-68. doi: 10.1016/j.nut.2018.05.034. Epub 2018 Jul 11.

Vitamin D deficiency and mild to moderate anemia in young North Indian children: A secondary data analysis.

Chowdhury R, Taneja S, Bhandari N, Strand TA, Bhan MK.
India, Norway

OBJECTIVES:
The aim of this study was to examine the association between vitamin D deficiency and anemia status among young children in the resource-poor setting of northern urban India.

METHODS:
We used data from a randomized controlled trial of daily supplementation with folic acid, vitamin B_{12}, or both for 6 mo in children 6 to 30 mo of age conducted in Delhi, India. We measured serum vitamin D status, hemoglobin, plasma vitamin B_{12}, folate, soluble transferrin receptor, and homocysteine levels at baseline. Children with severe anemia (hemoglobin [Hgb] <7 g/dL) were excluded from enrollment. Multivariable logistic and multinomial logistic regressions were used to examine the association between vitamin D and anemia status at baseline.

RESULTS:
25-Hydroxyvitamin-D (25 OHD) concentration was measured for 960 (96%) children. Of the children, 331 (34.5%) were vitamin-D deficient (<10 ng/mL). Approximately 70% of the enrolled children were anemic, with ~46% having moderate (Hgb 7-9.9 g/dL) and 24% mild (Hgb 10-10.9 g/dL) anemia. **There was no association between vitamin D and anemia status after adjusting for confounders; however, the risk for moderate anemia was significantly higher among vitamin D-deficient children than those who were vitamin-D replete (relative risk, 1.58; 95% confidence interval, 1.09-2.31).**

CONCLUSIONS:
Vitamin D deficiency was associated with moderate anemia among young children and the effect was independent of iron deficiency. The causal association of vitamin D deficiency with anemia risk remains debatable. The role of vitamin D in risk for anemia needs to be examined in further studies.

Health Technol Assess. 2019 Jan;23(2):1-44. doi: 10.3310/hta23020. (Open access available)

Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis.

Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Janssens W, Jensen ME, Kerley CP, Laaksi I,

Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S, Stelmach I, Trilok Kumar G, Urashima M, Camargo CA, Griffiths CJ, Hooper RL.
UK, USA, Sweden, Israel, Italy, Canada, New Zealand, Belgium, Australia, Ireland, Finland, Poland, India, Japan

BACKGROUND:
Randomised controlled trials (RCTs) exploring the potential of vitamin D to prevent acute respiratory infections have yielded mixed results. Individual participant data (IPD) meta-analysis has the potential to identify factors that may explain this heterogeneity.
OBJECTIVES:
To assess the overall effect of vitamin D supplementation on the risk of acute respiratory infections (ARIs) and to identify factors modifying this effect.
DATA SOURCES:
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and the International Standard Randomised Controlled Trials Number (ISRCTN) registry.
STUDY SELECTION:
Randomised, double-blind, placebo-controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration having incidence of acute respiratory infection as a prespecified efficacy outcome were selected.
STUDY APPRAISAL:
Study quality was assessed using the Cochrane Collaboration Risk of Bias tool to assess sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data, evidence of selective outcome reporting and other potential threats to validity.

RESULTS:
We identified 25 eligible RCTs (a total of 11,321 participants, aged from 0 to 95 years). IPD were obtained for 10,933 out of 11,321 (96.6%) participants. **Vitamin D supplementation reduced the risk of ARI among all participants [adjusted odds ratio (aOR) 0.88, 95% confidence interval (CI) 0.81 to 0.96; heterogeneity $p < 0.001$]. Subgroup analysis revealed that protective effects were seen in individuals receiving daily or weekly vitamin D without additional bolus doses (aOR 0.81, 95% CI 0.72 to 0.91), but not in those receiving one or more bolus doses (aOR 0.97, 95% CI 0.86 to 1.10; $p = 0.05$).** Among those receiving daily or weekly vitamin D, protective effects of vitamin D were stronger in individuals with a baseline 25-hydroxyvitamin D [25(OH)D] concentration of < 25 nmol/l (aOR 0.30, 95% CI 0.17 to 0.53) than in those with a baseline 25(OH)D concentration of ≥ 25 nmol/l (aOR 0.75, 95% CI 0.60 to 0.95; $p = 0.006$). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (aOR 0.98, 95% CI 0.80 to 1.20; $p = 0.83$). The body of evidence contributing to these analyses was assessed as being of high quality.
LIMITATIONS:
Our study had limited power to detect the effects of vitamin D supplementation on the risk of upper versus lower respiratory infection, analysed separately.
CONCLUSIONS:
Vitamin D supplementation was safe, and it protected against ARIs overall. Very deficient individuals and those not receiving bolus doses experienced the benefit. Incorporation of

additional IPD from ongoing trials in the field has the potential to increase statistical power for analyses of secondary outcomes.

Yaws

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

Int J Prev Med. 2018 Oct 12;9:88. doi: 10.4103/ijpvm.IJPVM_367_17. eCollection 2018. (Open access available)

A Randomized Controlled Trial of Zinc Supplementation as Adjuvant Therapy for Dengue Viral Infection in Thai Children.

Rerksuppaphol S, Rerksuppaphol L.
Thailand

Background:
Zinc deficiency is common in developing countries and increases the risk for several infectious diseases. Low serum zinc levels have been reported in children with dengue virus infection (DVI). This study aimed to assess the effects of zinc supplementation on DVI outcomes.

Methods:
A double-blinded, randomized trial was conducted in 50 children with dengue fever (DF)/dengue hemorrhagic fever admitted to the pediatric unit of MSMC Srinakharinwirot University Hospital, Thailand, between January 2016 and April 2017. **Bis-glycinate zinc or placebo was orally administered three times a day for 5 days or until defervescence**. The primary outcome was to evaluate the DVI defervescence phase; the secondary outcome was to assess hospitalization length and presence of severe DVI and zinc deficiency.

Results:
The mean time of defervescence was 29.2 ± 24.0 h in the supplementation group and 38.1 ± 31.5 h in the placebo group (*P* = 0.270). Meantime of hospital staying was 62.5 ± 23.8 h in the supplementation group and 84.7 ± 34.0 h in placebo group with the mean difference of hospital staying between groups of 22.2 h (95% confidence interval [CI]: 5.5-38.5 h; *P* = 0.010). Overall prevalence of zinc deficiency was 46%. Serum zinc levels increased from baseline to the end of the study. the mean gain was 26.4 µg/dL (95% CI: 13.6-39.1 µg/dL) in the supplementation group and 14.4 µg/dL (95% CI: 7.4-21.3 µg/dL) in placebo group. No signs of severe DVI were observed in both groups. Zinc supplementation was well tolerated.

Conclusions:
Overcoming zinc deficiency among Thai children may reduce DF duration and limit the hospitalization, in addition to other advantages that normal serum zinc levels have on overall children health.

Nutr J. 2018 Sep 15;17(1):86. doi: 10.1186/s12937-018-0391-5. (Open access available)

Efficacy of high zinc biofortified wheat in improvement of micronutrient status, and prevention of morbidity among preschool children and women - a double masked, randomized, controlled trial.

Sazawal S, Dhingra U, Dhingra P, Dutta A, Deb S, Kumar J, Devi P, Prakash A.
India

BACKGROUND:
Biofortification of staple food crops with zinc (Zn) can be one of the cost-effective and sustainable strategies to combat zinc deficiency and prevent morbidity among the target population. Agronomic approaches such as application of Zn fertilizers to soil and/or foliar spray seem to be a practical tool for Zn biofortification of wheat. However, there is a need to evaluate its efficacy from randomized controlled trials. This study aimed to evaluate the efficacy of zinc biofortified wheat flour on zinc status and its impact on morbidity among children aged 4-6 years and non-pregnant non lactating woman of child bearing age (WCBA) in Delhi, India.

METHODS:
In a community based, double-masked randomized controlled trial, 6005 participants (WCBA and child pairs) were enrolled and randomly allocated to receive either high zinc biofortified wheat flour (HZn, 30 ppm zinc daily) or low zinc biofortified wheat flour (LZn, 20 ppm zinc daily) for 6 months (WCBA @ 360 g/day and children @ 120 g/day). Baseline and endline blood samples were obtained for assessing hematological markers; zinc status and data on compliance and morbidity were collected.

RESULTS:
Compliance rates were high; ~ 88% of the WCBAs in both the groups consumed 50% or more of recommended amount of biofortfied wheat flour during the follow up. Similarly 86.9% children in HZn and 87.5% in LZn consumed 50% or more of recommended wheat flour intake. There was no significant difference in mean zinc levels between the groups at end study. This observation might be due to a marginal difference in zinc content (10 ppm) between the HZn and LZn wheat flour, and a short intervention period. **However a positive impact of bio-fortification on self-reported morbidity was observed. Compared to children in LZn group, children in HZn group had 17% (95% CI: 6 to 31%, p = 0.05) and 40% (95% CI: 16 to 57%; p = 0.0019) reduction in days with pneumonia and vomiting respectively.** WCBA in the HZn group also showed a statistically significant 9% fewer days with fever compared to LZn group.

CONCLUSIONS:
Biofortified wheat flour had a good compliance among children and WCBAs. Significant improvement on some of the self-reported morbidity indicators suggests that evaluating longer-term effects of biofortification with higher grain zinc content would be more appropriate.

Indian Pediatr. 2019 Mar 17. pii: S097475591600129. [Epub ahead of print]

Zinc Supplementation for Promoting Growth in Children Under 5 Years of age in Low- and Middle-income Countries: A Systematic Review.

Gera T, Shah D, Sachdev HS.

OBJECTIVE:
To study the effect of zinc supplementation on anthropometry and prevalence of malnutrition in children under 5 years of age.
DESIGN:
Systematic review of randomized controlled trials and cluster randomized trials.
SETTING:
Low- and middle-income countries (LMICs).
PARTICIPANTS:
63 trials with zinc supplementation, incorporating data on 27372 children. Trials conducted exclusively in specifically diseased participants and in children with severe acute malnutrition were excluded.
INTERVENTION:
Zinc supplementation, provided either as medicinal supplementation or through food fortification.
OUTCOME MEASURES:
(i) Anthropometry: weight, height, weight-for-height, mid-arm circumference, head circumference; (ii) Prevalence of malnutrition.
RESULTS:
There was no evidence of effect on height-for-age Z score at the end of supplementation period (25 trials; 9165 participants; MD= 0.00 Z; 95% CI -0.07, 0.07; P=0.98; moderate quality evidence) with significant heterogeneity (I^2 = 57%; P<0.001) related to dose and duration of zinc between trials. There was little or no effect on change in height-for-age Z score (13 trials; 8852 participants; MD= 0.11 Z; 95% CI -0.00, 0.21; P=0.05), but the heterogeneity was considerable (I^2=94%; P<0.001). There was no evidence of effect on length (6303 participants; MD= 1.18 cm; 95% CI -0.63, 2.99 cm, P=0.20; moderate quality evidence; considerable heterogeneity, I^2=99%) but a little positive effect on change in length (19 trials; 10783 participants; MD= 0.43 cm; 95% CI 0.16, 0.70, P=0.002; moderate quality evidence; considerable heterogeneity, I^2=93%). There was no evidence of effect on weight-for-age Z score or change in weight-for-age Z score but a little positive effect on weight (19 trials; 8851 study participants; MD= 0.23 kg; 95% CI 0.03, 0.42; P=0.02; considerable heterogeneity, I^2=91%) and change in weight (kg) (23 trials; 10143 study participants; MD= 0.11 kg; 95% CI 0.05, 0.17, P<0.001, substantial heterogeneity, I^2=80%). There was no evidence of effect on

weight-for-height Z score, and mid upper arm circumference at the end of supplementation period, but there was a little positive effect on change in MUAC from baseline (8 trials; 1724 participants; MD = 0.09 cm; 95% CI 0.01, 0.16; P=0.03; no heterogeneity, I^2=0%). Head circumference in zinc supplemented group was marginally higher compared to control (2966 study participants; MD= 0.39 cm; 95% CI 0.03, 0.75; P=0.03; substantial heterogeneity, I^2=67%). There was no evidence of benefit in stunting (10 trials; 11838 study participants; RR= 1.0; 95% CI 0.95, 1.06; P=0.89; Moderate Quality Evidence; no significant heterogeneity, I^2=11%), wasting (7 trials; 8988 study participants; RR= 0.94; 95% CI 0.82, 1.06; P=0.31; Moderate Quality Evidence; no significant heterogeneity, I^2=13%) or underweight (7 trials; 8677 study participants; RR= 1.08; 95% CI 0.96, 1.21; P=0.19; Moderate Quality Evidence; substantial heterogeneity, I^2=73%).
CONCLUSION:
Available evidence suggests that zinc supplementation probably leads to little or no improvement in anthropometric indices and malnutrition (stunting, underweight and wasting) in children under five years of age in LMICs. Advocating zinc supplementation as a public health measure to improve growth, therefore appears unjustified in these settings with scarce resources.

Nutrients. 2018 Dec 27;11(1). pii: E47. doi: 10.3390/nu11010047. (Open access available)

Impact of Two Forms of Daily Preventive Zinc or Therapeutic Zinc Supplementation for Diarrhea on Hair Cortisol Concentrations Among Rural Laotian Children: A Randomized Controlled Trial.

Hinnouho GM, Bernstein RM, Barffour MA, Arnold CD, Wessells KR, Ratsavong K, Bounheuang B, Kounnavong S, Hess SY.
USA, Laos

Abstract
Zinc supplementation has been shown to reduce the morbidity burden among young children, and may reduce chronic stress. Hair cortisol has been promoted as an indicator of chronic stress. We assessed the impact of different strategies for delivering supplementary zinc on hair cortisol concentrations (HCC) in young Laotian children and examined risk factors associated with HCC. In a randomized double-blind controlled trial (NCT02428647), children aged 6-23 mo were randomized to one of four intervention groups and followed for ~36 weeks: **daily preventive zinc (PZ) tablets (7 mg/day), daily multiple micronutrient powder (MNP) sachets (containing 10 mg zinc and 14 other micronutrients), therapeutic zinc (TZ) supplements for diarrhea treatment (20 mg/day for 10 days) or daily placebo powder**. HCC of 512 children was assessed at baseline and endline. ANCOVA and linear regression models were used to assess group differences in HCC and to examine the risk factors associated with HCC, respectively. At enrollment, mean HCC was 28.8 ± 43.9 pg/mg. In models adjusted for age at enrollment, health district, and baseline HCC there was no overall effect of the interventions on endline HCC and change in HCC. When controlling for additional predetermined covariates, there was a marginally significant effect on change in HCC (p = 0.075) with a slightly lower reduction of HCC in TZ compared to PZ (mean change (95% CI): -4.6 (-7.0; -2.3) vs. -9.4 (-11.7; -7.0) pg/mg; p = 0.053). At baseline, consumption of

iron rich foods was negatively associated with HCC, whereas AGP (α1-acid glycoprotein) levels, elevated AGP and C-reactive protein and high soluble transferrin receptor were positively associated with HCC. **In young Laotian children, MNP, PZ and TZ had no impact on HCC. The marginal difference in change in HCC between the PZ and TZ groups was too small to be considered of health significance.**