

# **RANDOMISED TRIALS IN CHILD AND ADOLESCENT HEALTH IN DEVELOPING COUNTRIES**

15<sup>th</sup> Edition  
July 2016-June 2017

[www.ichrc.org](http://www.ichrc.org)

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### SEARCH STRATEGY

Pubmed Advanced strategy, search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR Asia-Pacific) and (Child\*)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) publication date between July 1<sup>st</sup> 2016 and June 30<sup>th</sup> 2017.

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

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

**This year 235 studies were identified.** These were conducted in 61 countries from all regions of the world. Several trials from 2016-17 will lead to significant changes in child health recommendations.

The web-link for papers that are available in full-text on the Internet free of charge (**131 with free on-line access**) are included. Through HINARI (<http://www.who.int/hinari/en/>) a program set up by WHO in collaboration with publishers, the full-text versions of over 14,000 journal titles and 30,000 e-books are available to health institutions in over 100 countries. If your health institution (medical school, teaching hospital, nursing school, government office) has not registered with HINARI, you can check your eligibility and register online.

Please feel free to distribute this booklet to any colleagues. The previous editions (2002-2016) are available at: [www.ichrc.org](http://www.ichrc.org)

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

### **A brief summary of some of the important results in 2016-17**

- In a large trial involving 10,750 children from 8626 households in rural Malawi, use of biomass-fuelled cook stoves and a solar panel did not substantially reduce the incidence of pneumonia. This is somewhat similar to the results of a similar intervention in Guatemala, published in 2011, where overall pneumonia cases were not significantly reduced, but there were significant reductions in cases of severe clinical pneumonia with hypoxaemia, and severe RSV negative pneumonia.

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- In a trial of 60 children with fluid refractory septic shock in India, adrenaline (epinephrine) at 0.1-0.3 mcg/kg/min was more effective than dopamine at high doses (10-20mcg/kg/min) in resolving shock and avoiding organ dysfunction.
- Among Indian children with iron deficiency anaemia, levels of malondialdehyde, a biomarker of oxidative stress, were elevated and anti-oxidant enzymes lower compared with controls. After 8 weeks of iron therapy levels of antioxidants increased, and the biomarker of oxidative stress significantly reduced.
- A trial of 60 children with acute watery diarrhoea found that the probiotic *Saccharomyces boulardii* reduced the duration of diarrhoea and hospitalisation.
- In West Africa, ZMapp, a combination of 3 monoclonal antibodies against the glycoprotein of Ebola virus was associated with a lower death rate in recipients 8 of 36 (22%) compared with 13 of 35 patients (37%) who received the current standard of care alone, but this fell short of pre-specified levels of significance.
- Among 40 Indian children with epilepsy that was refractory to 2 anti-epileptic drugs, use of the Atkins diet (a modified ketogenic diet) were significantly more likely to have 50% and 90% in reductions in seizure frequency than 40 children on their normal diet.
- In HIV treatment clinics in Zambia, the designation of a quality improvement officer role among existing staff increased the proportion of patients receiving a three-month refill supply of antiretroviral drugs.
- In Malawi, among infants with a diagnosis of clinically suspected pneumocystis pneumonia, empirical use of steroids in the first 48 hours in addition to conventional TMP/SMX therapy significantly reduced mortality in hospital and 6 months after discharge.
- Among more than 700 HIV infected children over 3 years of age, on ART for an average of 2 years, continuing cotrimoxazole throughout childhood reduced skin infections. This adds to the trials in recent years showing benefits of ongoing cotrimoxazole shown against bacterial pneumonia, and is consistent with the WHO recommendation.
- In a trial of 1200 HIV exposed infants, those who were allocated to formula feeding had a higher incidence of oral colonisation with Gram negative bacteria than those allocated to breast feeding.
- In HIV-infected mothers at 14 or more weeks gestation, use of zidovudine-based ART as part of Option B+ resulted in a lower rate of very preterm delivery and significantly fewer infant deaths than a tenofavir-based ART, and both regimens of ART (Option B+) resulted in lower risk of vertical transmission of HIV than a traditional PMTCT regimen based on zidovudine and single-dose nevirapine.
- Among HIV-infected mothers in Malawi and South Africa, higher rates of maternal adherence to ART reduced the risk of detectable HIV RNA in breast milk, and undetectable breast milk HIV RNA reduced vertical transmission. This study underlined the importance of adherence to Option B+ in making breast feeding safe.
- Among Kenyan school children, 4 monthly treatment with albendazole reduced soil transmitted helminth infections from 50-60% down to 5-6%. Four-monthly treatment was more effective than annual treatment. And in a controlled trial in Peru, mebendazole proved safe with no more adverse events than placebo.
- In Iran, in a series of studies which ran for 13 years, treatment of visceral leishmaniasis with meglumine antimoniate for 1 week after fever defervescence was not inferior, and an acceptable alternative to the standard 28-day course for patients who showed a response to antimonial therapy. In these studies fever resolution was validated as a marker of drop in parasite density, and the studies were done in a region with low level of meglumine antimoniate resistance.

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- In rural Tanzania, trained and supervised drug dispensers performed and sold malaria rapid diagnostic tests (RDTs) under real market conditions to two-thirds of patients with suspected malaria, increasing the evidence-based prescriptions of artemisinin-based therapy. And in rural Uganda, RDTs used by community health workers also increased the rational prescribing of artemisinin-based treatment for malaria. However CHWs often failed to refer children who may have required hospital treatment.
- In Malawi insecticide treated bed nets had a population-based effect on malaria prevalence, i.e. even protecting children who were not sleeping under one, by reducing malaria transmission.
- In the Democratic Republic of the Congo intermittent prevention of malaria with sulfadoxine-pyrimethamine plus piperaquine protected children against anaemia, malaria parasitemia and clinical malaria more than sulfadoxine-pyrimethamine alone. In Senegal in a cluster randomised trial, seasonal malarial chemoprophylaxis with sulfadoxine-pyrimethamine plus amodiaquine substantially reduced the incidence of outpatient cases of malaria and of severe malaria in children, and reduced overall malaria transmission in the population.
- In Zambia, after 2 rounds of a mass drug administration program with dihydroartemisinin plus piperaquine, the 5-month cumulative infection incidence was 70% lower and 58% lower in lower- and higher-transmission areas, respectively, compared with control areas. In asymptomatic low-density gametocyte carriers with *P. falciparum* who were G6PD-normal, a single of primaquine substantially reduced carriage, and likely reduces transmission.
- Among Ugandan children given monthly chemoprophylaxis with dihydroartemisinin-piperaquine malaria episodes were 55% lower overall, and 97% lower if they were highly adherent. This protection continued into the year after chemoprophylaxis, perhaps because of specific T-cell activation that produces cytokines which are protective against malaria.
- In children with uncomplicated malaria in Burkina Faso, Kenya, and Tanzania, the rate of adequate clinical and parasitological response was 91% in those treated with artesunate-mefloquine and 90% in those treated with artemether-lumefantrine (AL). So artesunate-mefloquine is a potentially important drug against malaria in Africa.
- WHO now recommends adding a single low-dose of the gametocytocidal drug primaquine to AL for uncomplicated *P. falciparum* malaria as part of pre-elimination or elimination programs. This was tested in Tanzania among 110 patients with malaria and found to be as effective in curing acute malaria as AL alone.
- In Mozambique, a phase II trial of adjunctive rosiglitazone, a proliferator-activated receptor-gamma agonist, in children with uncomplicated malaria showed it to be well tolerated and without side effects. Further trials are underway.
- Among Ethiopian children with *P. vivax* malaria who were G6PD-normal, the risk of recurrence of vivax was 5-fold lower if treated with chloroquine or artemether-lumefantrine *plus* 14 days of primaquine, than with chloroquine or artemether-lumefantrine alone. In this population chloroquine was more effective than AL.
- Among women with mild-moderate anaemia attending an antenatal clinic in India, intravenous iron sucrose was more effective than oral iron in increasing ferritin, serum iron and haemoglobin.
- In 40 Indian children with acute bacterial meningitis, pre-treatment with single dose rifampin (a non-bacteriolytic but still bacteriocidal antibiotic) 30 minutes before ceftriaxone administration reduced the markers of inflammation and neuronal damage in the CSF compared with children who received only ceftriaxone (a bactericidal and bacteriolytic antibiotic).

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- Among 1124 girls from 8 rural Ugandan schools, the provision of puberty education and sanitary pads had some effect on reducing the dropout in school attendance.
- In India, community health volunteers were more effective if they were supervised by a paid community health worker, and in Uganda when community health workers were trained in using malaria rapid diagnostic tests, they referred more children than CHWs who treated presumptively for malaria based on symptoms without testing.
- In 2017 mobile phones were used in trials for public health education in many areas: in China knowledge and behaviour towards rabies; improving vaccination coverage by reminders sent from village doctors; and improving compliance of caregivers with a home food fortification and nutrition program. In Ecuador mobile phone messages to post-natal mothers improved breastfeeding, attendance at ante-natal check-ups, and contraceptive use. Trials are underway in Guinea Bissau of using mobile phones to increase measles vaccination coverage, in India to improve MCH attendance, and in Kenya to improve adherence to Option B+ antiretroviral therapy.
- In 540 Nepali newborns, delayed umbilical cord clamping group significantly reduced the risk of iron deficiency, and improved haemoglobin by an average of 0.3 g per dL at 12 months of age. The differences were small, but this is the first RCT showing a reduction in iron deficiency *anaemia* from delayed cord clamping.
- In a study in Colombia, 20 years after the first RCT of Kangaroo Mother Care, 69% of the initial 716 participants were followed up. The early effects of KMC were still present in the most fragile individuals; and parents who used KMC in the initial trial were more protective and nurturing 20 years on. There was reduced school absenteeism and reduced hyperactivity, aggressiveness, externalization, and socio-deviant conduct of young people who as newborns received KMC.
- Among 326 newborns in India, delivered in either hospital or outside a health facility, cord cleansing with 4% chlorhexidine soon after birth significantly reduced bacterial colonization at 48 hours, compared with placebo or dry cord care.
- In Bangladesh, prenatal and postnatal supplementation of mothers with small-quantity lipid-based nutrient supplements during the first 1000 days improved child linear growth and head size, and a positive effect on motor and language development. In Ghana lipid-based nutrient supplements increased linear growth at 18 months...But in Malawi lipid-based nutrient supplements did not increase children's physical activity as measured by "mean vector magnitude counts" per 15 seconds!
- In Morocco, using biscuits fortified with iron and EDTA lowered blood lead levels compared with controls among children at risk of environmental lead poisoning.
- In Bangladesh and Vietnam the "Alive and Thrive" program aimed at encouraging breast feeding, with intensified interpersonal counselling, mass media, and community mobilization increased population-based breast feeding rates.
- In Nepal a program to improve home food production consisting of a home garden, poultry raising, and nutrition education over 2.5 years reduced anaemia among mothers and children, reduced the prevalence of underweight among mothers, but had no effect on children's growth compared to families without such a home food program. A similar village-based agricultural program in rural Cambodia increased dietary diversity, particularly the consumption of vitamin A rich foods, fruits and vegetables, but evaluation may be too early to show an effect on child growth.
- In Philippines, a conditional cash transfer program of the Philippine government called 'Pantawid', significantly reduced the prevalence of stunting among 241 children in intervention areas compared with 244 children in control areas. Pantawid, which is modelled on similar programs in Brazil and Mexico, aims to eradicate extreme poverty in the Philippines by investing in health and education. Other conditional and



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unconditional cash transfer programs reported in trials this year from Burkina Faso (no effect on wasting) and Pakistan (reduced wasting at 6 months, but not at older age) had more modest effects.

- Among 319 children being treated in Chile for cancer who developed febrile neutropenia, if positive for a respiratory virus and negative for a bacterial pathogen and with a favourable evolution after 48 hours of antimicrobial therapy, withholding further antimicrobials was just as safe as continuing antibiotics, and this reduced antibiotic exposure and hospital stay.
- Among patients with chemical ocular burns in India, application of topical umbilical cord serum resulted in faster epithelialisation than standard medical therapy.
- In communities with high tuberculosis and HIV prevalence in South Africa and Zimbabwe, active surveillance for TB using GeneXpert MTB/RIF resulted in a higher proportion of patients with culture-positive tuberculosis being commenced on treatment at 60 days (86%) compared to people identified by active surveillance without the use of Xpert (56% commenced within 60 days). Whether there are resources for Xpert or not, active community based surveillance with symptom screening and sputum smears is effective in identifying unrecognised TB in endemic communities. Identifying children with TB by community-based active surveillance is also possible, especially for school-aged children, but because young children are mostly smear negative or cannot produce sputum, this requires symptom based screening and clinical assessment.
- In children aged 2 to 17 years in Dominican Republic, Panama, and the Philippines, a phase II trial involving a 2 dose schedule, 3 months apart, of a tetravalent Dengue vaccine induced levels of antibodies that are likely to be protective against all 4 Dengue virus serotypes. Whether this vaccine protects against severe Dengue in children under 9 years of age is uncertain.
- Among over 5000 healthy Chinese infants and children aged 6-35 months, 2 doses of the Vigoo enterovirus 71 (EV71) vaccine generated high levels of protective antibodies and provided substantial protection against hand-foot-and-mouth disease during a 2 year follow-up period.
- In large trials of over 21,000 women in Costa Rica and Brazil, HPV16/18 vaccine protected against infection from a variety of oncogenic and non-oncogenic strains, and virus type replacement did not occur among vaccinated individuals within four years of being vaccinated. Two other trials in 2017 suggested that 2 doses in boys and girls aged 9-14 were just as effective in generating protective antibody responses as a 3 dose schedule in adult women.
- In Mali maternal influenza vaccine provides some protection against influenza in infants in the first 6 months of life, however the protection was only 33-37%, and there was a higher rate of presumed neonatal sepsis in the influenza vaccinated group.
- In Thailand and the Philippines, the Japanese Encephalitis Chimeric vaccine provided long-term protective immunity for over 60% of 596 children 5 years after primary vaccination at 12-18 months of age, and a booster dose of the vaccine given after 5 years sero-protected all children.
- In Niger oral bovine pentavalent rotavirus vaccine had an efficacy of 67% against severe rotavirus gastroenteritis among infants who received three doses of the vaccine at 6, 10, and 14 weeks of age. In Malawi the efficacy of oral rotavirus vaccine was 49% and in South Africa it was 77% against severe rotavirus diarrhoea, however because of the greater burden of rotavirus in Malawi, more cases were prevented. In Bangladesh, 2 doses of human rotavirus vaccine at 6 and 10 weeks had an effectiveness against acute rotavirus diarrhoea among vaccinated children of 41%, and an efficacy of 29% among the entire villages where the rotavirus vaccine. In a small study involving data from 4

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African countries, live oral rotavirus vaccine was immunogenic and appeared to be safe in HIV infected children.

- In Ghanaian children with yaws, a single oral dose of azithromycin (30mg/kg), was not inferior to a single dose of intramuscular benzathine penicillin (50,000 IU) for the treatment of early yaws, providing clinical cure in 98% of cases after 3 weeks. This is a similar to a previous RCT from Papua New Guinea.

Again this year many 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. Some trials *are* large scale and definitive, and add to previous trials that have results in the same direction: for example two trials this year involving over 20,000 breast-fed infants found no clinically significant benefit of a neonatal dose of vitamin A.

I have been liberal in what is included as an RCT. Many papers are the reports of sub-studies within an RCT, they may be cohort or background studies, rather than the primary results of the completed RCT. Some papers are published RCT methodologies on planned studies, which I have put at the end of each topic section.

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.

In the last 15 years there have been **2418 trial publications** summarised in the editions of this booklet. The public health benefits that have come from the trials on malaria, for example can be seen in the uptake of new interventions and reductions in malaria in each affected country in the world. The funding of comprehensive programs of research to “roll-back” malaria and implement the results of trials is a good example of the optimum benefit of research. The changes to HIV treatment is another example of public health which has benefited remarkably from randomised trials: the improvements to prevention of mother-to-child transmission being a primary example. While malaria and HIV rates are falling reductions of similar magnitudes are

## **Randomised trials in child health in developing countries 2016-17**

not being seen in pneumonia, tuberculosis, malnutrition or neonatal illness – and taking similar comprehensive approaches to the research agenda and to research-driven public health interventions are needed.

The evolving complexity of child health in the 21<sup>st</sup> Century requires that research should also evolve. It is encouraging to see the evaluation of the developmental, psychological and mental health effects of interventions. Also encouraging are the increased number of trials that include adolescents, the recognition of maternal nutrition and physical and mental health to infant outcomes, and trials of various ways to improve education. Clinical trials again this year from India and China tackled issues related to non-communicable diseases, including myopia, obesity, oral health and cancer. However research gaps 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 hospitals.

More support is needed for clinical research capacity in low income countries. The increasing research output from transitional countries is welcome and reflects the ‘grand convergence’, but may mean that the child health priorities in the countries with the greatest health burdens are over-shadowed. More than ever a focus on understanding and reducing inequity is needed if child health is to improve, and clinician and public health researchers have a role to play in this.

Trevor Duke  
August 2017

### **Acknowledgement**

Thanks to Charlotte for help with editing

## Acute respiratory infection

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

### Prevention of pneumonia

[Lancet](#). 2017 Jan 14;389(10065):167-175. doi: 10.1016/S0140-6736(16)32507-7. Epub 2016 Dec 7.

**A cleaner burning biomass-fuelled cookstove intervention to prevent pneumonia in children under 5 years old in rural Malawi (the Cooking and Pneumonia Study): a cluster randomised controlled trial.**

[Mortimer K](#)<sup>1</sup>, [Ndamala CB](#)<sup>2</sup>, [Naunje AW](#)<sup>2</sup>, [Malava J](#)<sup>3</sup>, [Katundu C](#)<sup>3</sup>, [Weston W](#)<sup>4</sup>, [Havens D](#)<sup>5</sup>, [Pope D](#)<sup>6</sup>, [Bruce NG](#)<sup>6</sup>, [Nyirenda M](#)<sup>7</sup>, [Wang D](#)<sup>5</sup>, [Crampin A](#)<sup>7</sup>, [Grigg J](#)<sup>8</sup>, [Balmes J](#)<sup>9</sup>, [Gordon SB](#)<sup>4</sup>.

#### **BACKGROUND:**

WHO estimates exposure to air pollution from cooking with solid fuels is associated with over 4 million premature deaths worldwide every year including half a million children under the age of 5 years from pneumonia. We hypothesised that replacing open fires with cleaner burning biomass-fuelled cookstoves would reduce pneumonia incidence in young children.

#### **METHODS:**

We did a community-level open cluster randomised controlled trial to compare the effects of a cleaner burning biomass-fuelled cookstove intervention to continuation of open fire cooking on pneumonia in children living in two rural districts, Chikhwawa and Karonga, of Malawi. Clusters were randomly allocated to intervention and control groups using a computer-generated randomisation schedule with stratification by site, distance from health centre, and size of cluster. Within clusters, households with a child under the age of 4.5 years were eligible. Intervention households received two biomass-fuelled cookstoves and a solar panel. The primary outcome was WHO Integrated Management of Childhood Illness (IMCI)-defined pneumonia episodes in children under 5 years of age. Efficacy and safety analyses were by intention to treat. The trial is registered with ISRCTN, number ISRCTN59448623.

#### **FINDINGS:**

We enrolled 10 750 children from 8626 households across 150 clusters between Dec 9, 2013, and Feb 28, 2016. 10 543 children from 8470 households contributed 15 991 child-years of follow-up data to the intention-to-treat analysis. The IMCI pneumonia incidence rate in the intervention group was 15.76 (95% CI 14.89-16.63) per 100 child-years and in the control group 15.58 (95% CI 14.72-16.45) per 100 child-years, with an intervention versus control incidence rate ratio (IRR) of 1.01 (95% CI 0.91-1.13; p=0.80). Cooking-related serious adverse events (burns) were seen in 19 children; nine in the intervention and ten (one death) in the control group (IRR 0.91 [95% CI 0.37-2.23]; p=0.83).

#### **INTERPRETATION:**

We found no evidence that an intervention comprising cleaner burning biomass-fuelled cookstoves reduced the risk of pneumonia in young children in rural Malawi. Effective strategies to reduce the adverse health effects of household air pollution are needed.

Free access: [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)32507-7/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32507-7/fulltext)

[Trop Med Int Health](#). 2017 Feb;22(2):187-195. doi: 10.1111/tmi.12820. Epub 2017 Jan 5.

**Household-level risk factors for secondary influenza-like illness in a rural area of Bangladesh.**

[Weaver AM](#)<sup>1,2</sup>, [Khatun-E-Jannat K](#)<sup>3</sup>, [Cercione E](#)<sup>1</sup>, [Krytus K](#)<sup>1</sup>, [Sohel BM](#)<sup>3</sup>, [Ahmed M](#)<sup>3</sup>, [Rahman M](#)<sup>3</sup>, [Azziz-Baumgartner E](#)<sup>4</sup>, [Yu J](#)<sup>1</sup>, [Fry AM](#)<sup>4</sup>, [Luby SP](#)<sup>3,5</sup>, [Ram PK](#)<sup>1</sup>.

**OBJECTIVE:**

To describe household-level risk factors for secondary influenza-like illness (ILI), an important public health concern in the low-income population of Bangladesh.

**METHODS:**

Secondary analysis of control participants in a randomised controlled trial evaluating the effect of handwashing to prevent household ILI transmission. We recruited index-case patients with ILI - fever (<5 years); fever, cough or sore throat (≥5 years) - from health facilities, collected information on household factors and conducted syndromic surveillance among household contacts for 10 days after resolution of index-case patients' symptoms. We evaluated the associations between household factors at baseline and secondary ILI among household contacts using negative binomial regression, accounting for clustering by household.

**RESULTS:**

Our sample was 1491 household contacts of 184 index-case patients. Seventy-one percentage reported that smoking occurred in their home, 27% shared a latrine with one other household and 36% shared a latrine with >1 other household. A total of 114 household contacts (7.6%) had symptoms of ILI during follow-up. Smoking in the home (RR<sub>adj</sub> 1.9, 95% CI: 1.2, 3.0) and sharing a latrine with one household (RR<sub>adj</sub> 2.1, 95% CI: 1.2, 3.6) or >1 household (RR<sub>adj</sub> 3.1, 95% CI: 1.8-5.2) were independently associated with increased risk of secondary ILI.

**CONCLUSION:**

Tobacco use in homes could increase respiratory illness in Bangladesh. The mechanism between use of shared latrines and household ILI transmission is not clear. It is possible that respiratory pathogens could be transmitted through faecal contact or contaminated fomites in shared latrines.

## Treatment of pneumonia

(Where there were topic headings from previous years under which no trials were published in 2016-17, I have left the sub-heading in the book. Not all topic sub-headings have equal importance in the overall burden of childhood disease, and some topics are not in need of further trials, but over time it is reflective of research priorities and gaps.)

Otitis media

Bronchiolitis

Upper respiratory tract infections, tonsillitis

## Adolescent health

(See also Vaccines - HPV vaccine and Injury prevention)

[PLoS One](#). 2016 Dec 21;11(12):e0166122. doi: 10.1371/journal.pone.0166122. eCollection 2016.

[Menstruation and the Cycle of Poverty: A Cluster Quasi-Randomised Control Trial of Sanitary Pad and Puberty Education Provision in Uganda.](#)

[Montgomery P](#)<sup>1</sup>, [Hennegan J](#)<sup>1</sup>, [Dolan C](#)<sup>2</sup>, [Wu M](#)<sup>3</sup>, [Steinfeld L](#)<sup>4</sup>, [Scott L](#)<sup>5</sup>.

### BACKGROUND:

Poor menstrual knowledge and access to sanitary products have been proposed as barriers to menstrual health and school attendance. In response, interventions targeting these needs have seen increasing implementation in public and private sectors. However, there has been limited assessment of their effectiveness.

### OBJECTIVES:

Assess the impact of providing reusable sanitary pads and puberty education on girls' school attendance and psychosocial wellbeing outcomes.

### METHODS:

A cluster quasi-randomised controlled trial was conducted across 8 schools, including 1124 girls, in rural Uganda. Schools were allocated to one of four conditions: the provision of puberty education alone; reusable sanitary pads alone; puberty education and reusable sanitary pads; and a control (no intervention). The primary outcome was school attendance. Secondary outcomes reflected psychosocial wellbeing.

### RESULTS:

At follow-up, school attendance had worsened for girls across all conditions. Per-protocol analysis revealed that this decline was significantly greater for those in the control condition  $d = 0.52$  (95%CI 0.26-0.77), with those in control schools having a 17.1% (95%CI: 8.7-25.5) greater drop in attendance than those in any intervention school. There were no differences between the intervention conditions. High rates of school drop-out and transfer meant the trial suffered from substantial participant drop-out. Intention-to-treat analyses using two different imputation strategies were consistent with the main results, with mean differences of 5.2% attendance in best-case and 24.5% in worst-case imputations. Results were robust to adjustments for clustering. There was no impact of the interventions on girls' self-reported shame or insecurity during menstruation.

### CONCLUSION:

Results of the trial support the hypothesised positive impact of providing sanitary pads or puberty education for girls' school attendance in a developing country context. Findings must be

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interpreted with caution in light of poor participant retention, intervention fidelity, and the attendance measures used.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5176162/>

[BMC Public Health](#). 2017 Apr 17;17(1):322. doi: 10.1186/s12889-017-4245-4.

**[Effect of the PREPARE intervention on sexual initiation and condom use among adolescents aged 12-14: a cluster randomised controlled trial in Dar es Salaam, Tanzania.](#)** Mmbaga EJ<sup>1</sup>, Kajula L<sup>2</sup>, Aarø LE<sup>3,4</sup>, Kilonzo M<sup>2</sup>, Wubs AG<sup>3</sup>, Eggers SM<sup>5</sup>, de Vries H<sup>5</sup>, Kaaya S<sup>2</sup>.

### BACKGROUND:

Unsafe sexual practices continue to put adolescents at risk for a number of negative health outcomes in Tanzania. While there are some effective theory-based intervention packages with positive impact on important mediators of sexual behaviours, a context specific and tested intervention is urgently needed in Tanzania.

### PURPOSE:

To develop and evaluate an intervention that will have a significant effect in reducing sexual initiation and promoting condom use among adolescents aged 12-14 in Dar es Salaam, Tanzania.

### DESIGN:

A school-based Cluster Randomised Controlled Trial was conducted during 2011-2014 in Kinondoni Municipality.

### METHODS:

A total of **38 public primary schools** were randomly selected, of which half were assigned to the intervention and half to the control group based on their size and geographic location. Participants were interviewed using a self-administered questionnaire at baseline before the PREPARE intervention and then, 6 and 12 months following intervention. **The primary outcomes were self-reported sex initiation and condom use during the past 6 months.** Data analysis was done using Generalized Estimating Equation (GEE) modelling controlling for repeated measures and clustering of students within schools.

### RESULTS:

A total of 5091 students were recruited at baseline, and interviewed again at 6 (n = 4783) and 12 months (n = 4370). Mean age of participants at baseline was 12.4 years. Baseline sociodemographic, psychometric and behavioural characteristics did not significantly differ between the two study arms. The GEE analysis indicated that the intervention had a significant effect on sexual initiation in both sexes after controlling for clustering and correlated repeated measures. A significantly higher level of action planning to use condoms was reported among female adolescent in the intervention arm than those in the control arm (p = 0.042). An effect on condom use behaviour was observed among male adolescent (p = 0.004), but not among female (p = 0.463).

### CONCLUSIONS:

**The PREPARE intervention had an effect in delaying self-reported sexual initiation among adolescents aged 12-14 in Dar es Salaam Tanzania.** The intervention positively influenced action planning to use condoms for both sexes and increased actual condom use among male adolescents only. Future interventions addressing adolescent sexual and reproductive health should focus on impacting mediators of behaviour change.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5392916/>

### Comment

*The PREPARE intervention involved three interactive teaching components, one implemented by teachers, one by peer educators, and one by health care providers during adolescents' visits to youth health service clinics.*

[Am J Public Health](#). 2016 Aug;106(8):1439-41. doi: 10.2105/AJPH.2016.303225. Epub 2016 May 19.

### **Formative Work and Community Engagement Approaches for Implementing an HIV Intervention in Botswana Schools.**

[Miller KS](#)<sup>1</sup>, [Cham HJ](#)<sup>1</sup>, [Taylor EM](#)<sup>1</sup>, [Berrier FL](#)<sup>1</sup>, [Duffy M](#)<sup>1</sup>, [Vig J](#)<sup>1</sup>, [Chipazi L](#)<sup>1</sup>, [Chakalisa C](#)<sup>1</sup>, [Sidibe S](#)<sup>1</sup>, [Swart K](#)<sup>1</sup>, [Tau NS](#)<sup>1</sup>, [Clark LF](#)<sup>1</sup>.

### **Abstract**

Providing adolescents with evidence-based sexual risk reduction interventions is critical to addressing the HIV/AIDS epidemic among adolescents in sub-Saharan Africa. Project AIM (Adult Identity Mentoring) is an innovative, evidence-based, youth development intervention that is being evaluated for the first time in Botswana through a 3-year (2015-2017), 50-school cluster randomized controlled trial, including testing for herpes simplex virus type 2 as a sexual activity biomarker. Conducting a trial of this magnitude requires the support and collaboration of government and community stakeholders. All school staff, including teachers, must be well informed about the study; dedicated staff placed at each school can help to improve school and community familiarity with the study, improve the information flow, and relieve some of the burden study activities places on schools.

[Glob Health Sci Pract](#). 2017 Mar 28;5(1):115-137. doi: 10.9745/GHSP-D-16-00215. Print 2017 Mar 24.

### **Preventing Peer Violence Against Children: Methods and Baseline Data of a Cluster Randomized Controlled Trial in Pakistan.**

[McFarlane J](#)<sup>1</sup>, [Karmaliani R](#)<sup>2</sup>, [Maqbool Ahmed Khuwaja H](#)<sup>2</sup>, [Gulzar S](#)<sup>2</sup>, [Somani R](#)<sup>2</sup>, [Saeed Ali T](#)<sup>2</sup>, [Somani YH](#)<sup>2</sup>, [Shehzad Bhamani S](#)<sup>2</sup>, [Krone RD](#)<sup>3</sup>, [Paulson RM](#)<sup>3</sup>, [Muhammad A](#)<sup>4</sup>, [Jewkes R](#)<sup>5</sup>.

### **BACKGROUND:**

Violence against and among children is a global public health problem that annually affects 50% of youth worldwide with major impacts on child development, education, and health including increased probability of major causes of morbidity and mortality in adulthood. It is also associated with the experience of and perpetration of later violence against women. The aim of this article is to describe the intervention, study design, methods, and baseline findings of a cluster randomized controlled trial underway in Pakistan to evaluate a school-based play intervention aiming to reduce peer violence and enhance mental health.

### **METHODS:**

A cluster randomized controlled design is being conducted with boys and girls in grade 6 in 40 schools in Hyderabad, Pakistan, over a period of 2 years. The Multidimensional Peer-Victimization and Peer Perpetration Scales and the Children's Depression Inventory 2 (CDI 2) are being used to measure the primary outcomes while investigator-derived scales are being used to assess domestic violence within the family. Specifics of the intervention, field logistics, ethical, and fidelity management issues employed to test the program's impact on school age youth in a volatile and politically unstable country form this report.

### **BASELINE RESULTS:**



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A total of 1,752 school-age youth were enrolled and interviewed at baseline. Over the preceding 4 weeks, 94% of the boys and 85% of the girls reported 1 or more occurrences of victimization, and 85% of the boys and 66% of the girls reported 1 or more acts of perpetration. Boys reported more depression compared with girls, as well as higher negative mood and self-esteem scores and more interpersonal and emotional problems.

### INTERPRETATION:

Globally, prevalence of youth violence perpetration and victimization is high and associated with poor physical and emotional health. Applying a randomized controlled design to evaluate a peer violence prevention program built on a firm infrastructure and that is ready for scale-up and sustainability will make an important contribution to identifying evidence-informed interventions that can reduce youth victimization and perpetration.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5478222/>

[Asia Pac J Public Health](#). 2016 Nov;28(8):765-775.

### Effectiveness of Mindfulness Intervention on Psychological Behaviors Among Adolescents With Parental HIV Infection: A Group-Randomized Controlled Trial.

[Mon MM](#)<sup>1,2</sup>, [Liabsuetrakul T](#)<sup>2</sup>, [Htut KM](#)<sup>3</sup>.

#### Abstract

This study aims to identify the effectiveness of mindfulness intervention on the psychological behaviors of adolescents with parental HIV infection and its associated factors in Myanmar. A total of 80 adolescents from 2 intervention townships and 80 adolescents from 2 control townships were enrolled in a group randomized controlled trial with assessments at baseline and 6 months follow-up. The mindfulness intervention involved monthly group sessions for 3 consecutive months led by an experienced mindfulness trainer. Three domains of psychological behaviors-namely, emotional, conduct, and social behaviors-were assessed at baseline and compared after 6 months. Multilevel regression analysis was used to determine the effectiveness of the intervention and associated factors for psychological behaviors. The intervention significantly improved emotional and conduct behaviors at 6 months ( $P < .001$ ) but had no effect on social behavior. The significant effect of the intervention existed after adjusting for gender, family type, child age, and orphan status.

[J Tradit Complement Med](#). 2016 Apr 20;7(1):99-105. doi: 10.1016/j.jtcme.2016.03.001. eCollection 2017 Jan.

### Effect of yoga program on executive functions of adolescents dwelling in an orphan home: A randomized controlled study.

[Purohit SP](#)<sup>1</sup>, [Pradhan B](#)<sup>1</sup>.

#### Abstract

Executive function (EF) is important for physical and mental health of children. Studies have shown that children with poverty and early life stress have reduced EF. The aim of the study was to evaluate the effect of Yoga program on the EF of orphan adolescents. Seventy two apparently healthy orphan adolescents randomized and allocated into two groups as Yoga group ( $n = 40$ ; 14 girls, age =  $12.69 \pm 1.35$  yrs) and Wait List Control (WLC) group ( $n = 32$ , 13 girls, age =  $12.58 \pm 1.52$  yrs). Yoga group underwent three months of Yoga program in a schedule of 90 min per day, four days per week whereas the WLC group followed the routine activities. They were assessed by Stroop Color-Word Task, Digit Symbol Substitution Test (DSST), Digits Span Test and Trail Making Test (TMT) at the beginning and end of the program. The repeated

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measures ANOVA showed significant difference in time and group interactions ( $p < 0.05$ ) for all subtests of Stroop Color-Word Task and Digit Span Test and part-A of TMT whereas there were no significant difference found in DSST and TMT (part-B). The post-hoc test with Bonferroni adjustment also showed significant improvements ( $p < 0.001$ ) within the Yoga group in all test scores while in wrong score of DSST did not exhibit significant reduction. Whereas the WLC group, showed significant improvement ( $p < 0.05$ ) in Stroop Color, Color-Word score, net score of DSST, Digit Span forward and Digit Span Total. Three months Yoga program was found useful for the young orphan adolescents in improving their executive functions.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5198826/>

## Allergy

(See Vitamin D, skin disease)

## Anaemia and iron deficiency

(See also Nutrition – micronutrients and food fortification)

[J Nutr.](#) 2016 Aug;146(8):1601-8. doi: 10.3945/jn.115.227462. Epub 2016 Jul 13.

[Tubaramure, a Food-Assisted Integrated Health and Nutrition Program in Burundi, Increases Maternal and Child Hemoglobin Concentrations and Reduces Anemia: A Theory-Based Cluster-Randomized Controlled Intervention Trial.](#)

[Leroy JL](#)<sup>1</sup>, [Olney D](#)<sup>2</sup>, [Ruel M](#)<sup>2</sup>.

### BACKGROUND:

Despite their popularity, food-assisted maternal and child health and nutrition (MCHN) programs have not been evaluated rigorously, and evidence of their impacts on maternal and child outcomes is scant.

### OBJECTIVE:

This study estimated the impact of Tubaramure, a food-assisted MCHN program implemented by Catholic Relief Services and partners in eastern Burundi, on hemoglobin and anemia (primary outcome) in children aged 0-23.9 mo and their mothers and explored the impact pathways. The program targeted women and their children during their first 1000 d of life and included 1) food rations, 2) strengthening and promotion of the use of health services, and 3) behavior change communication.

### METHODS:

This was a cluster-randomized controlled study to assess program impact by using cluster fixed-effects double-difference models with repeated cross-sectional data (baseline and follow-up 2 y later). We explored impact pathways by estimating impact on intermediary factors addressed by Tubaramure that are known determinants of hemoglobin and anemia and by regressing hemoglobin and anemia on each determinant to assess the plausibility that the effect operated through each determinant.

### RESULTS:

Hemoglobin decreased and anemia increased markedly from baseline to follow-up, but Tubaramure had a significant ( $P < 0.05$ ) beneficial effect on both children [6.1 percentage points (pps)] and mothers who had given birth in the previous 3 mo (34.9 pps). The program also had significant ( $P < 0.05$ ) impacts on factors along the hypothesized impact pathways: dietary diversity, consumption of iron-rich foods, morbidity, and fever for child hemoglobin and dietary diversity, consumption of iron-rich foods, and current bed-net use for maternal anemia.

### CONCLUSIONS:

We showed, for the first time to our knowledge, that a food-assisted MCHN program had a positive impact on anemia and hemoglobin in both mothers and children. The plausible pathways identified highlight the importance of addressing multiple determinants of anemia. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01072279) as [NCT01072279](https://clinicaltrials.gov/ct2/show/study/NCT01072279).

### Comment

*The Tubaramure program involves provision of pre- and post-natal care services, support for the national IMCI program, growth monitoring, treatment of severe acute malnutrition and improving households practices in nutrition, hygiene and maternal and childhood illnesses.*

[BMC Pediatr.](https://doi.org/10.1186/s12887-016-0689-4) 2016 Sep 1;16(1):149. doi: 10.1186/s12887-016-0689-4.

**Efficacy and safety of hepcidin-based screen-and-treat approaches using two different doses versus a standard universal approach of iron supplementation in young children in rural Gambia: a double-blind randomised controlled trial.**

[Wegmüller R](#)<sup>1</sup>, [Bah A](#)<sup>2</sup>, [Kendall L](#)<sup>3</sup>, [Goheen MM](#)<sup>4</sup>, [Mulwa S](#)<sup>3</sup>, [Cerami C](#)<sup>5</sup>, [Moretti D](#)<sup>6</sup>, [Prentice AM](#)<sup>2</sup>.

### BACKGROUND:

Iron deficiency prevalence rates frequently exceed 50% in young children in low-income countries. The World Health Organization (WHO) recommended universal supplementation of young children where anaemia rates are >40 %. However, large randomized trials have revealed that provision of iron to young children caused serious adverse effects because iron powerfully promotes microbial growth. Hepcidin - the master regulator of iron metabolism that integrates signals of infection and iron deficiency - offers the possibility of new solutions to diagnose and combat global iron deficiency. We aim to evaluate a hepcidin-screening-based iron supplementation intervention using hepcidin cut-offs designed to indicate that an individual requires iron, is safe to receive it and will absorb it.

### METHODS:

The study is a proof-of-concept, three-arm, double blind, randomised controlled, prospective, parallel-group non-inferiority trial. Children will be randomised to receive, for a duration of 12 weeks, one of three multiple micronutrient powders (MNP) containing: A) 12 mg iron daily; B) 12 mg or 0 mg iron daily based on a weekly hepcidin screening indicating if iron can be given for the next seven days or not; C) 6 mg or 0 mg iron daily based on a weekly hepcidin screening indicating if iron can be given for the next seven days or not. The inclusion criteria are age 6-23 months, haemoglobin (Hb) concentration between 7 and 11 g/dL, z-scores for Height-for-Age, Weight-for-Age and Weight-for-Height > -3 SD and free of malaria. Hb concentration at 12 weeks will be used to test whether the screen-and-treat approaches are non-inferior to universal supplementation. Safety will be assessed using caregiver reports of infections, in vitro bacterial and *P. falciparum* growth assays and by determining the changes in the gut microbiota during the study period.

### DISCUSSION:

A screen-and-treat approach using hepcidin has the potential to make iron administration safer in areas with widespread infections. If this proof-of-concept study shows promising results the development of a point-of-care diagnostic test will be the next step.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5009643/>

### Comment

*Hepcidin is a amino acid peptide synthesized by the liver. It is the main iron regulatory hormone, it blocks the release of iron from enterocytes into the plasma. The rate of entry of iron into the plasma depends on the plasma level of hepcidin; when iron stores drop, the synthesis of hepcidin is down-regulated and enterocytes and macrophages release more iron. Reduced hepcidin levels occur in states of anaemia and hypoxia. When iron levels are high the synthesis of hepcidin increases and the release of iron from enterocytes and macrophages is diminished. The synthesis and release of hepcidin is also stimulated by bacterial lipopolysaccharide and cytokines, therefore hepcidin is an acute phase reactant. The gene regulating hepcidin synthesis is called HAMP.*

(Rossi E. *Hepcidin - the Iron Regulatory Hormone. Clin Biochem Rev. 2005 26: 47–49.*)

[J Clin Diagn Res.](#) 2016 Oct;10(10):SC13-SC19. Epub 2016 Oct 1.

### **Effect of Oral Iron on Markers of Oxidative Stress and Antioxidant Status in Children with Iron Deficiency Anaemia.**

[Zaka-Ur-Rab Z<sup>1</sup>](#), [Adnan M<sup>2</sup>](#), [Ahmad SM<sup>3</sup>](#), [Islam N<sup>4</sup>](#).

#### **INTRODUCTION:**

Conflicting reports are available on the relationship of Iron Deficiency Anaemia (IDA) and iron therapy with oxidative stress.

#### **AIM:**

To study the levels of markers of oxidative stress and anti-oxidant status in children with IDA and to assess the effect of iron therapy on the same.

#### **MATERIALS AND METHODS:**

This prospective, single centre, hospital based study was a sub-study of a randomized controlled trial conducted in the Department of Paediatrics, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh in collaboration with the Department of Biochemistry (of the same institution) between October 2009 to February 2011. The sub-study was conducted in two parts: in the first part, **levels of a biomarker of oxidative stress {Malondialdehyde (MDA)} and anti-oxidant enzymes {Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GPx)}** were assessed and compared between **67 children with IDA and 31 non-anaemic controls**; in the second part, **the effect of oral iron (6mg/kg/day) for eight weeks on these markers was studied in a subset of 35 children with IDA**. The Bivariate correlations procedure was used to compute pair wise associations for a set of variables. T-tests (Independent samples t-test/Paired sample t-test) and Non-parametric tests (Mann-Whitney test/Wilcoxon signed-rank test) were applied as applicable for normally and non-normally distributed data, respectively.

#### **RESULTS:**

**Levels of anti-oxidant enzymes were significantly lower ( $p<0.001$ ) in children with IDA as compared to controls**, viz., SOD {median, 8.63 (IQR, 8.60-8.66) vs. 9.46 (IQR, 9.14-9.62) units/mg protein}, CAT {median, 8.49 (IQR, 8.46-8.50) vs. 9.10 (IQR, 9.04-9.14)  $\mu\text{mol H}_2\text{O}_2/\text{min}/\text{mg protein}$ } and GPx {median, 49.19 (IQR, 48.99-49.60) vs. 56.94(IQR, 56.80-57.14)  $\text{mol NADPH oxidized}/\text{min}/\text{mg protein}$ }. Whereas, levels of MDA were significantly higher ( $p<0.001$ ) in IDA group {median, 1.50 (IQR, 1.48-1.52) vs. 1.24 (IQR, 1.20-1.27) moles/ml of serum}. Levels of Haemoglobin (Hb) and markers of iron status (serum iron, transferrin saturation and ferritin) had a very strong, highly significant positive correlation ( $p<0.001$ ) with levels of anti-oxidant enzymes (SOD, CAT, and GPx) but a very strong, highly significant negative correlation ( $p<0.001$ ) with MDA. Total Iron Binding Capacity (TIBC) on the other hand, had a strong, highly significant ( $p<0.001$ ) negative correlation with SOD, CAT, and GPx but a strong, highly significant positive correlation ( $p<0.001$ ) with MDA. **After eight weeks of daily iron therapy, a highly significant rise ( $p<0.001$ ) from baseline was observed**

in levels of SOD, CAT, and GPx in subjects with IDA. On the other hand, MDA levels declined significantly ( $p < 0.001$ ).

**CONCLUSION:**

**Lipid peroxidation is increased and anti-oxidant defenses lowered in IDA. These changes, however, may be mitigated effectively with oral iron therapy.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5121754/>

**Comment**

*Lipid peroxidation is the process in which free radicals attack unsaturated fatty acids in a lipid membrane. Cell membranes can be damaged.*

[Clin Nutr.](#) 2017 Aug;36(4):986-991. doi: 10.1016/j.clnu.2016.07.002. Epub 2016 Jul 18.

**Supplementation of vitamin B12 or folic acid on hemoglobin concentration in children 6-36 months of age: A randomized placebo controlled trial.**

[Kumar T](#)<sup>1</sup>, [Taneja S](#)<sup>2</sup>, [Sachdev HPS](#)<sup>3</sup>, [Refsum H](#)<sup>4</sup>, [Yajnik CS](#)<sup>5</sup>, [Bhandari N](#)<sup>2</sup>, [Strand TA](#)<sup>6</sup>; [Study Group](#).

**BACKGROUND & AIMS:**

The main objective of this report is to measure to what extent folate or vitamin B12 given daily for 6 months to young North Indian Children improves hemoglobin (Hb) concentration.

**METHODS:**

In a randomized placebo controlled trial in low-to-middle income neighborhoods in New Delhi, India, **children were randomized into four groups in a 1:1:1:1 ratio and supplemented daily for 6 months with 2 RDAs of vitamin B12, folic acid, both, or placebo.** All children with anemia at baseline were given iron supplementation daily for 2 months. We measured the plasma concentrations of soluble transferrin receptor (sTfR), folate, vitamin B12, total homocysteine (tHcy) and Hb in 262 children.

**RESULTS:**

Mean Hb concentration decreased in all four study groups during the six months of follow up and supplementation of either or both of the vitamins did not improve the Hb concentration. Iron supplements for the initial 2 mo had limited effect on anemia at 6 mo as almost 90% were still anemic at study end.

**CONCLUSION:**

**Supplementation of folic acid and/or vitamin B12 for 6 months does not improve Hb concentration in young children.** Our findings do not argue for widespread vitamin B12 or folic acid supplementation to combat anemia. Our results also call for alternative strategies to improve iron status and treat iron deficiency anemia.

[Am Heart J.](#) 2017 Jan;183:129-136. doi: 10.1016/j.ahj.2016.01.007. Epub 2016 Jan 21.

**B-type natriuretic peptide and plasma hemoglobin levels following transfusion of shorter-storage versus longer-storage red blood cells: Results from the TOTAL randomized trial.**

[Dhabangi A](#)<sup>1</sup>, [Ainomugisha B](#)<sup>2</sup>, [Cserti-Gazdewich C](#)<sup>3</sup>, [Ddungu H](#)<sup>4</sup>, [Kyeyune D](#)<sup>5</sup>, [Musisi E](#)<sup>5</sup>, [Opoka R](#)<sup>6</sup>, [Stowell CP](#)<sup>7</sup>, [Dzik WH](#)<sup>8</sup>.

**BACKGROUND:**

Prior studies have suggested that transfusion of stored red blood cells (RBCs) with increased levels of cell-free hemoglobin might reduce the bioavailability of recipient nitric oxide (NO) and cause myocardial strain.



### METHODS:

Ugandan children (ages 6-60 months) with severe anemia and lactic acidosis were randomly assigned to receive RBCs stored 1-10 days versus 25-35 days. B-type natriuretic peptide (BNP), vital signs, renal function test results, and plasma hemoglobin were measured. Most children had either malaria or sickle cell disease and were thus at risk for reduced NO bioavailability.

### RESULTS:

Seventy patients received RBCs stored 1-10 days, and 77 received RBCs stored 25-35 days. The median (interquartile range) cell-free hemoglobin was nearly 3 times higher in longer-storage RBCs (26.4 [15.5-43.4]  $\mu\text{mol/L}$ ) than in shorter-storage RBCs (10.8 [7.8-18.6]  $\mu\text{mol/L}$ ),  $P < .0001$ . Median (interquartile range) BNP 2 hours posttransfusion was 156 (59-650) pg/mL (shorter storage) versus 158 (59-425) pg/mL (longer storage),  $P = .76$ . BNP values 22 hours posttransfusion were 110 (46-337) pg/mL (shorter storage) versus 96 (49-310) pg/mL (longer storage),  $P = .76$ . Changes in BNP within individuals from pretransfusion to 2 hours (or 22 hours) posttransfusion were not significantly different between the study groups. BNP change following transfusion did not correlate with the concentration of cell-free hemoglobin in the RBC supernatant. Blood pressure, blood urea nitrogen, creatinine, and change in plasma hemoglobin were not significantly different in the 2 groups.

### CONCLUSION:

In a randomized trial among children at risk for reduced NO bioavailability, we found that BNP, blood pressure, creatinine, and plasma hemoglobin were not higher in patients receiving RBCs stored for 25-35 versus 1-10 days.

## Anaesthesia and intensive care

(see also Asthma)

[Paediatr Anaesth.](#) 2017 Jan;27(1):37-44. doi: 10.1111/pan.13010. Epub 2016 Oct 13.

**[Comparison of oral midazolam with intranasal dexmedetomidine premedication for children undergoing CT imaging: a randomized, double-blind, and controlled study.](#)**

[Ghai B](#)<sup>1</sup>, [Jain K](#)<sup>1</sup>, [Saxena AK](#)<sup>2</sup>, [Bhatia N](#)<sup>1</sup>, [Sodhi KS](#)<sup>2</sup>.

### BACKGROUND:

Children undergoing computerized tomography (CT) frequently require sedation to allay their anxiety, and prevent motion artifacts and stress of intravenous (IV) cannulation.

### AIMS:

The aim of this trial was to compare the effectiveness of oral midazolam and intranasal dexmedetomidine as sole premedicants in children for carrying out both IV cannulation as well as CT scanning, without the need for additional IV sedatives.

### METHODS:

Fifty-nine children, aged 1-6 years, scheduled to undergo CT imaging under sedation were **randomized to receive either 0.5 mg·kg<sup>-1</sup> oral midazolam (group M) or 2.5 mcg·kg<sup>-1</sup> intranasal dexmedetomidine (group D)**. After 20-30 min, intravenous cannulation was performed and response to its placement was graded using the Groningen Distress Rating Scale (GDRS). After cannulation, children were transferred on the CT table, and **assessed using the Ramsay sedation score (RSS)**. CT imaging was performed without any further sedative if the RSS was  $\geq 4$ . If there was movement or decrease in sedation depth ( $\text{RSS} \leq 3$ ), ketamine 1 mg·kg<sup>-1</sup> IV was given as an initial dose, followed by subsequent doses of 0.5 mg·kg<sup>-1</sup> IV if required.

### RESULTS:

A Significantly higher proportion of children in group D (67%) achieved  $\text{RSS} \geq 4$  as compared to group M (24%) ( $P=0.002$ ). The risk ratio (95% CI) was 2.76 (1.38-5.52). Significantly lower

GDRS scores were noted in group D (1(1-2)) as compared to group M (2(1-2)) at the time of venipuncture ( $P = 0.04$ ).

**CONCLUSION:**

**In the doses and time intervals used in our study, intranasal dexmedetomidine ( $2.5 \mu\text{g}\cdot\text{kg}^{-1}$ ) was found to be superior to oral midazolam ( $0.5 \text{mg}\cdot\text{kg}^{-1}$ ) for producing satisfactory sedation for CT imaging.**

**Efficacy of dexmedetomidine as an adjuvant to ropivacaine in pediatric caudal epidural block.**

Kamal M<sup>1</sup>, Mohammed S<sup>1</sup>, Meena S<sup>1</sup>, Singariya G<sup>1</sup>, Kumar R<sup>1</sup>, Chauhan DS<sup>1</sup>.

**CONTEXT:**

Caudal analgesia is a reliable and an easy method to provide intraoperative and postoperative analgesia for infraumbilical surgeries in pediatric population but with the disadvantage of short duration of action after single injection. Many additives were used in combination with local anesthetics in the caudal block to prolong the postoperative analgesia.

**AIM:**

We compared the analgesic effects and side effects of dexmedetomidine added to ropivacaine in pediatric patients undergoing lower abdominal surgeries.

**SETTINGS AND DESIGN:**

Double-blinded randomized controlled trial.

**MATERIALS AND METHODS:**

Sixty patients (2-10 years) were evenly and randomly assigned into two groups in a double-blinded manner. After sevoflurane in oxygen anesthesia, **each patient received a single caudal dose of ropivacaine 0.25% (1 ml/kg) combined with either dexmedetomidine  $2 \mu\text{g}/\text{kg}$  in normal saline 0.5 ml, or corresponding volume of normal saline** according to group assignment. Hemodynamic variables, end-tidal sevoflurane, and emergence time were monitored. Postoperative analgesia, requirement of additional analgesic, sedation, and side effects were assessed during the first 24 h.

**RESULTS:**

The duration of postoperative analgesia was significantly longer ( $P = 0.001$ ) and total consumption of rescue analgesic was significantly lower in Group RD compared with Group R ( $P < 0.05$ ). Group RD have better quality of sleep and prolonged duration of sedation ( $P = 0.001$ ). No significant difference was observed in the incidence of hemodynamic changes or side effects.

**CONCLUSION:**

**Addition of dexmedetomidine to caudal ropivacaine significantly prolongs analgesia in children undergoing lower abdominal surgeries without an increase in the incidence of side effects.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5044720/>

J Clin Anesth. 2016 Sep;33:322-9. doi: 10.1016/j.jclinane.2016.03.067. Epub 2016 May 19.

**Comparison of caudal epidural block and ultrasonography-guided transversus abdominis plane block for pain relief in children undergoing lower abdominal surgery.**

Sethi N<sup>1</sup>, Pant D<sup>2</sup>, Dutta A<sup>2</sup>, Koul A<sup>2</sup>, Sood J<sup>2</sup>, Chugh PT<sup>3</sup>.

**STUDY OBJECTIVE:**

## Randomised trials in child health in developing countries 2016-17

We conducted this study to compare the efficacy of **caudal epidural block (CEB) vs ultrasonography-guided transversus abdominis plane (TAP) block** for providing postoperative pain relief in children scheduled for lower abdominal surgery. Whereas the primary objective was to compare the duration of postoperative analgesia, the secondary objectives included comparative assessment (TAP vs CEB) of quality of pain relief in the first 24 hours postoperatively and rescue analgesia requirements.

### DESIGN:

Randomized-control, prospective, observer-blinded, 2-arm, single-center comparison.

### SETTING:

Operating room, postoperative recovery area.

### PATIENTS:

Eighty-children, aged 2-6 years, of American Society of Anesthesiologists physical status I/II scheduled to undergo unilateral lower abdominal surgery under general anesthesia.

### INTERVENTIONS:

The recruited children were randomly allocated to receive under **general anesthesia either CEB (group C, 0.75 mL/kg of 0.25% bupivacaine) or ultrasonography-guided administration of TAP block (group T, 0.5 mL/kg of 0.25% bupivacaine).**

### MEASUREMENTS:

Intraoperative: heart rate and noninvasive blood pressure; postoperative: pain profile, including duration of postoperative analgesia, quality of pain relief, and rescue analgesia requirements.

### MAIN RESULTS:

**The median duration of postoperative analgesia was significantly greater in children who received CEB than those who were administered TAP block (group C: 362.5 minutes [172.5-693.75] vs group T: 210 minutes [108.75-362.5];  $P < .05$ ).** No difference was found in the incidence of postoperative pain up to 6 hours from the point of initiation of assessment (group C: 47.2% vs group T: 55.9%;  $P > .05$ ). **The children who received CEB experienced greater incidence of pain in the 6- to 24-hour postoperative interval than those administered TAP block (group C: 75% vs group T: 44.1%;  $P < .05$ ).** Although there was no difference in the rescue analgesia requirements, the number of children not requiring any rescue analgesia in the first 24 hours postoperatively was significantly higher in the TAP group (group C:  $n=2$  vs group T:  $n=8$ ;  $P < .05$ ).

### CONCLUSIONS:

In children undergoing lower abdominal surgery, CEB provides a significantly prolonged duration of postoperative analgesia when compared with ultrasonography-guided TAP block.

[Reg Anesth Pain Med.](#) 2016 Sep-Oct;41(5):610-5. doi: 10.1097/AAP.0000000000000447.  
**Pudendal Versus Caudal Block in Children Undergoing Hypospadias Surgery: A Randomized Controlled Trial.**

[Kendigelen P<sup>1</sup>](#), [Tutuncu AC](#), [Emre S](#), [Altindas F](#), [Kaya G](#).

### BACKGROUND AND OBJECTIVES:

Postoperative pain management after hypospadias surgery is often challenging. Caudal block is used for analgesia but has limitations. This study compares the analgesic efficiency of pudendal block with that of caudal block in pediatric patients undergoing hypospadias repair surgery.

### METHODS:

This prospective, double-blind, randomized, controlled study enrolled 84 patients receiving pudendal block or caudal block before hypospadias surgery. In the pudendal group, the pudendal nerve was identified using a nerve stimulator, and the block consisted of 0.25% bupivacaine 0.5 mL/kg. In the caudal group, the caudal block used 0.2% bupivacaine 1 mL/kg. Our primary



outcome was pain intensity within 24 hours postoperatively. The trial was registered at ClinicalTrials.gov (number: [NCT02390388](https://clinicaltrials.gov/ct2/show/study/NCT02390388)).

**RESULTS:**

For the primary outcome, **patients in the pudendal group had lower postoperative pain intensity when compared with the caudal group ( $P < 0.001$ )**. Three patients in the pudendal group and all of the patients in the caudal group needed additional analgesia within 24 hours after the surgery ( $P < 0.001$ ). The family satisfaction rate was significantly higher in the pudendal group ( $P < 0.001$ ).

**CONCLUSIONS:**

For the pudendal group, the pain scores for the first 24 hours after the surgery were significantly lower and the duration of analgesia was longer.

[Indian J Anaesth](#). 2017 Apr;61(4):326-331. doi: 10.4103/ija.IJA\_541\_15.

**Comparative evaluation of Airtraq™ optical Laryngoscope and Miller's blade in paediatric patients undergoing elective surgery requiring tracheal intubation: A randomized, controlled trial.**

[Das B<sup>1</sup>](#), [Samanta A<sup>2</sup>](#), [Mitra S<sup>1</sup>](#), [Jamil SN<sup>3</sup>](#).

**BACKGROUND AND AIMS:**

The Airtraq™ optical laryngoscope is the only marketed videolaryngoscope for paediatric patients besides the fibre-optic bronchoscope. We hypothesized that intubation would be easier with Airtraq™ compared to Miller blade. Hence, we compared Airtraq™ with the Miller laryngoscope as intubation devices in paediatric patients.

**METHODS:**

This prospective, randomized study was conducted in a tertiary care teaching hospital. Sixty children belonging to American Society of Anesthesiologists' Grade I-II, aged 2-10 years, posted for routine surgery requiring tracheal intubation were randomly allocated to undergo intubation using a Miller ( $n = 30$ ) or Airtraq™ ( $n = 30$ ) laryngoscope. The primary outcome measure was time of intubation. We also measured ease of intubation, number of attempts, percentage of glottic opening score (POGO), haemodynamic changes and airway trauma. Student t test was used to analyse parametric data.

**RESULTS:**

Intubation time was comparable between Miller's laryngoscope ( $15.13 \pm 1.33$ s) compared to Airtraq™ ( $11.53 \pm 0.49$  s) ( $P = 0.29$ ) **The number of first and second attempts at intubation were 25 and 5 for the Miller laryngoscope and 29 and 1 for the Airtraq™**. Median visual analogue score (VAS) for ease of intubation was 5 in Miller group compared to 3 in Airtraq™ group. The median POGO score was 75 in the Miller group and 100 in the Airtraq™ group ( $P = 0.01$ ). Haemodynamic changes were maximum and most significant immediately and 1 min after intubation. Airway trauma occurred in three patients (9.09%) in Miller group and one patient (3.33%) in Airtraq™ group.

**CONCLUSION:**

The Airtraq™ reduced the difficulty of tracheal intubation and degree of haemodynamic stimulation compared to the Miller laryngoscope in paediatric patients.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5416723/>

[Indian J Pediatr](#). 2017 Apr 5. doi: 10.1007/s12098-017-2335-z. [Epub ahead of print]

**Efficacy of Flippits to Reduce Pain in Children during Venipuncture - A Randomized Controlled Trial.**

[Risaw L](#)<sup>1</sup>, [Narang K](#)<sup>1</sup>, [Thakur JS](#)<sup>2</sup>, [Ghai S](#)<sup>1</sup>, [Kaur S](#)<sup>1</sup>, [Bharti B](#)<sup>3</sup>.

**OBJECTIVES:**

To investigate the **efficacy of distraction by flippits/distraction cards in relieving pain associated with pediatric venipuncture process in young children.**

**METHODS:**

This study was a prospective, non-blinded, randomized controlled trial. The sample consisted of 210 children aged 4 to 6 y undergoing phlebotomy in the sampling room of the Advanced Pediatric Center outpatient department and were randomly assigned to control and intervention groups. Latter were exposed to distraction using flippits/distraction cards during the procedure. Pain was assessed for both groups by using FLACC (Face Legs Activity Cry Consolability) behavior pain assessment scale. In addition, procedural pain was also assessed by Wong Bakers Faces Pain Scale (WBFPS) using children and parents' report.

**RESULTS:**

Flippits (distraction cards) had a significant effect on behavioral response to pain in children during blood sampling as evidenced by lower mean pain scores in the intervention group ( $2.75 \pm 0.97$ ) as compared to the control group ( $3.24 \pm 0.85$ ) as per FLACC behavioral pain assessment scale ( $p < 0.001$ ). Parents and self reported pain as per Wong Baker Faces Pain Scale was also lower in the intervention group as compared to the control group ( $p < 0.001$ ). Odds of severe pain/discomfort (total pain score 7-10) were 2.5 times higher in controls as compared to the intervention group (OR 2.5; 95% CI: 1.40-4.45) (P 0.002).

**CONCLUSIONS:**

The use of simple distraction technique using flippits can significantly relieve the pain associated with blood sampling in children.

## Intensive care

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

[Pediatr Crit Care Med.](#) 2016 Nov;17(11):e502-e512.

**Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock.**

[Ramaswamy KN](#)<sup>1</sup>, [Singhi S](#), [Jayashree M](#), [Bansal A](#), [Nallasamy K](#).

**OBJECTIVE:**

We compared efficacy of dopamine and epinephrine as first-line vasoactive therapy in achieving resolution of shock in fluid-refractory hypotensive cold septic shock.

**DESIGN:**

Double-blind, pilot, randomized controlled study.

**SETTING:**

Pediatric emergency and ICU of a tertiary care teaching hospital.

**PATIENTS:**

Consecutive children 3 months to 12 years old, with fluid-refractory hypotensive septic shock, were enrolled between July 2013 and December 2014.

**INTERVENTION:**

Enrolled children were randomized to receive either dopamine (in incremental doses, 10 to 15 to 20  $\mu\text{g/kg/min}$ ) or epinephrine (0.1 to 0.2 to 0.3  $\mu\text{g/kg/min}$ ) till end points of resolution of shock were achieved. After reaching maximum doses of test drugs, open-label vasoactive was started as per discretion of treating team. Primary outcome was resolution of shock within

## Randomised trials in child health in developing countries 2016-17

first hour of resuscitation. The study was registered (CTRI/2014/02/004393) and was approved by institute ethics committee.

### MEASUREMENTS AND MAIN RESULTS:

We enrolled 29 children in epinephrine group and 31 in dopamine group. **Resolution of shock within first hour was achieved in greater proportion of children receiving epinephrine (n = 12; 41%) than dopamine (n = 4; 13%) (odds ratio, 4.8; 95% CI, 1.3-17.2; p = 0.019); the trend persisted even at 6 hours (48.3% vs 29%; p = 0.184).** Children in epinephrine group had lower Sequential Organ Function Assessment score on day 3 (8 vs 12; p = 0.05) and more organ failure-free days (24 vs 20 d; p = 0.022). No significant difference in adverse events (16.1% vs 13.8%; p = 0.80) and mortality (58.1% vs 48.3%; p = 0.605) was observed between the two groups.

### CONCLUSION:

**Epinephrine is more effective than dopamine in achieving resolution of fluid-refractory hypotensive cold shock within the first hour of resuscitation and improving organ functions.**

## Antibiotic resistance

## Asthma and chronic lung disease

[Ann Thorac Med.](#) 2016 Oct-Dec;11(4):283-288.

**[Ketamine versus aminophylline for acute asthma in children: A randomized, controlled trial.](#)**

[Tiwari A](#)<sup>1</sup>, [Guglani V](#)<sup>1</sup>, [Jat KR](#)<sup>2</sup>.

### BACKGROUND:

There is a lack of consensus regarding second-line therapy in children with acute asthma who fail to the standard therapy. Ketamine had bronchodilator property and may be useful in the treatment of acute asthma.

### OBJECTIVE:

The objective of this study was to evaluate the efficacy and safety of ketamine as compared to aminophylline in children with acute asthma who respond poorly to the standard therapy.

### METHODS:

This randomized controlled trial included patients with acute asthma having Pediatric Respiratory Assessment Measure (PRAM) score  $\geq 5$  at 2 h of standard therapy. The enrolled **patients received either intravenous (IV) ketamine or IV aminophylline.** Primary outcome measure was change in PRAM score at the end of intervention. Secondary outcome measures included adverse effects, change in PO<sub>2</sub> and PCO<sub>2</sub>, need for mechanical ventilation, and duration of hospital stay.

### RESULTS:

The trial included 24 patients each in ketamine and aminophylline groups. The baseline parameters were similar between the groups. **The primary outcome was similar in both the groups with a change in PRAM score of  $4.00 \pm 1.25$  and  $4.17 \pm 1.68$  ( $P = 0.699$ ) in ketamine and aminophylline groups, respectively.** The secondary outcomes were not different between the groups.

### CONCLUSION:

Ketamine and aminophylline were equally effective for children with acute asthma who responded poorly to the standard therapy.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070438/>

## Community health workers and health education

[Reprod Health](#). 2016 Oct 3;13(1):126.

**[Supportive supervision for volunteers to deliver reproductive health education: a cluster randomized trial.](#)**

[Singh D](#)<sup>1</sup>, [Negin J](#)<sup>2</sup>, [Orach CG](#)<sup>3</sup>, [Cumming R](#)<sup>2</sup>.

### BACKGROUND:

Community Health Volunteers (CHVs) can be effective in improving pregnancy and newborn outcomes through community education. Inadequate supervision of CHVs, whether due to poor planning, irregular visits, or ineffective supervisory methods, is, however, recognized as a weakness in many programs. There has been little research on best practice supervisory or accompaniment models.

### METHODS:

From March 2014 to February 2015 a proof of concept study was conducted to compare **training alone versus training and supportive supervision by paid CHWs (n = 4) on the effectiveness of CHVs (n = 82) to deliver education about pregnancy, newborn care, family planning and hygiene**. The pair-matched cluster randomized trial was conducted in eight villages (four intervention and four control) in Budondo sub-county in Jinja, Uganda.

### RESULTS:

Increases in desired behaviors were seen in both the intervention and control arms over the study period. Both arms showed high retention rates of CHVs (95 %). **At 1 year follow-up there was a significantly higher prevalence of installed and functioning tippy taps for hand washing ( $p < 0.002$ ) in the intervention villages (47 %) than control villages (35 %). All outcome and process measures related to home-visits to homes with pregnant women and newborn babies favored the intervention villages.** The CHVs in both groups implemented what they learnt and were role models in the community.

### CONCLUSIONS:

A team of CHVs and CHWs can facilitate families accessing reproductive health care by addressing cultural norms and scientific misconceptions. **Having a team of 2 CHWs to 40 CHVs enables close to community access to information, conversation and services.**

Supportive supervision involves creating a non-threatening, empowering environment in which both the CHV and the supervising CHW learn together and overcome obstacles that might otherwise demotivate the CHV. While the results seem promising for added value with supportive supervision for CHVs undertaking reproductive health activities, further research on a larger scale will be needed to substantiate the effect.

### KEYWORDS:

Accompaniment; CHVs; CHWs; Community Health Volunteers; Community Health Workers; Empowerment; Maternal and Newborn Health; Neonatal health; Pregnancy; Supportive supervision

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5048471/>

[Science](#). 2016 Oct 7;354(6308). pii: aaf7384.

**The impact of training informal health care providers in India: A randomized controlled trial.**

Das J<sup>1,2</sup>, Chowdhury A<sup>3</sup>, Hussam R<sup>4</sup>, Banerjee AV<sup>5</sup>.

**Abstract**

Health care providers without formal medical qualifications provide more than 70% of all primary care in rural India. Training these informal providers may be one way to improve the quality of care where few alternatives exist. We report on a randomized controlled trial assessing a program that provided 72 sessions of training over 9 months to 152 informal providers (out of 304). Using standardized patients ("mystery clients"), we assessed clinical practice for three different conditions to which both providers and trainers were blinded during the intervention, representative of the range of conditions that these providers normally diagnose and treat. Training increased correct case management by 7.9 percentage points (14.2%) but did not affect the use of unnecessary medicines and antibiotics. At a program cost of \$175 per trainee, our results suggest that multitopic medical training offers an effective short-run strategy to improve health care.

Am J Trop Med Hyg. 2016 Dec 7;95(6):1398-1408. Epub 2016 Oct 31.

**Referral Patterns of Community Health Workers Diagnosing and Treating Malaria: Cluster-Randomized Trials in Two Areas of High- and Low-Malaria Transmission in Southwestern Uganda.**

Lal S<sup>1</sup>, Ndyomugenyi R<sup>2</sup>, Magnussen P<sup>3,4</sup>, Hansen KS<sup>5</sup>, Alexander ND<sup>5</sup>, Paintain L<sup>6</sup>, Chandramohan D<sup>6</sup>, Clarke SE<sup>6</sup>.

**Abstract**

Malaria-endemic countries have implemented community health worker (CHW) programs to provide malaria diagnosis and treatment to populations living beyond the reach of health systems. However, there is limited evidence describing the referral practices of CHWs. We examined the impact of malaria rapid diagnostic tests (mRDTs) on CHW referral in two cluster-randomized trials, one conducted in a moderate-to-high malaria transmission setting and one in a low-transmission setting in Uganda, between January 2010 and July 2012. All CHWs were trained to prescribe artemisinin-based combination therapy (ACT) for malaria and recognize signs and symptoms for referral to health centers. **CHWs in the control arm used a presumptive diagnosis for malaria based on clinical symptoms, whereas intervention arm CHWs used mRDTs.** CHWs recorded ACT prescriptions, mRDT results, and referral in patient registers. An intention-to-treat analysis was undertaken using multivariable logistic regression. Referral was more frequent in the intervention arm versus the control arm (moderate-to-high transmission,  $P < 0.001$ ; low transmission,  $P < 0.001$ ). Despite this increase, referral advice was not always given when ACTs or prereferral rectal artesunate were prescribed: 14% prescribed rectal artesunate in the moderate-to-high setting were not referred. In addition, CHWs considered factors alongside mRDTs when referring. Child visits during the weekends or the rainy season were less likely to be referred, whereas visits to CHWs more distant from health centers were more likely to be referred (low transmission only). **CHWs using mRDTs and ACTs increased referral compared with CHWs using a presumptive diagnosis.** To address these concerns, referral training should be emphasized in CHW programs as they are scaled-up.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5154457/>



[Am J Trop Med Hyg.](#) 2017 Feb 8;96(2):501-510. doi: 10.4269/ajtmh.16-0126. Epub 2016 Nov 28.

**Credit with Health Education in Benin: A Cluster Randomized Trial Examining Impacts on Knowledge and Behavior.**

# [Karlan D](#)<sup>1,2,3</sup>, [Thuysbaert B](#)<sup>4,2</sup>, [Gray B](#)<sup>5</sup>.

**Abstract**

We evaluate whether health education integrated into microcredit lending groups reduces health risks by improving health knowledge and self-reported behaviors among urban and rural borrowers in eastern Benin. In 2007, we randomly assigned 138 villages in the Plateau region of Benin to one of four variations of a group liability credit product, varying lending groups' gender composition and/or inclusion of health education using a  $2 \times 2$  design. Women in villages receiving health education, regardless of gender composition of the groups, showed improved knowledge of malaria and of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), but not of childhood illness danger signs. No significant changes in health behavior were observed except an increase in HIV/AIDS prevention behavior, a result predominantly driven by an increase in respondents' self-reported ability to procure a condom, likely an indicator of increased perceived access rather than improved preventative behavior. Women in villages assigned to mixed-gender groups had significantly lower levels of social capital, compared with villages assigned to female-only groups. This suggests there may be an important trade-off to consider for interventions seeking improved health outcomes and social capital through provision of services to mixed-gender groups. Although bundling health education with microcredit can expand health education coverage and lower service-delivery costs, the approach may not be sufficient to improve health behaviors.

[BMC Public Health.](#) 2017 Jan 19;17(1):95. doi: 10.1186/s12889-016-3991-z.

**Effects of community health volunteers on infectious diseases of children under five in Volta Region, Ghana: study protocol for a cluster randomized controlled trial.**

[Ma Y](#)<sup>1</sup>, [Kim H](#)<sup>2</sup>, [Cho Y](#)<sup>1</sup>, [Lee J](#)<sup>1</sup>, [Degley JK](#)<sup>3</sup>, [Adam AG](#)<sup>4</sup>, [Lee G](#)<sup>1</sup>, [Lee H](#)<sup>1</sup>, [Cha S](#)<sup>5,6</sup>.

**BACKGROUND:**

In many low- and middle-income countries, community health volunteers (CHVs) are employed as a key element of the public health system in rural areas with poor accessibility. However, few studies have assessed the effectiveness of CHVs in improving child health in sub-Saharan Africa through randomized controlled trials. The present study aims to measure the impact of health promotion and case management implemented by CHVs on the health of under-5 children in Ghana.

**METHODS/DESIGN:**

This study presents the protocol of a cluster-randomized controlled trial assessing the impacts of CHVs, in which the community was used as the randomization unit. A phase-in design will be adopted, and the intervention arm will be implemented in the intervention arm during the first phase and in the control arm during the second phase. **The key intervention is the deployment of CHVs, who provide health education, provide oral rehydration solutions and zinc tablets to children with diarrhea, and diagnose malaria using a thermometer and a rapid diagnostic test kit during home visits.** The primary endpoints of the study are the **prevalence of diarrhea and fever/malaria in children under 5 years of age, as well as the proportion of affected children receiving case management for diarrhea and malaria.** The first and second rounds of household surveys to collect data will be conducted in the first phase, and the final round will be conducted during the second phase.

**DISCUSSION:**

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With growing attention paid to the roles of CHVs as an essential part of the community health system in low-income countries, this study will contribute valuable information to the body of knowledge on the effects of CHVs.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5244532/>

## Dengue

(see Vaccines - dengue)

[PLoS Negl Trop Dis](#). 2016 Nov 7;10(11):e0005106. doi: 10.1371/journal.pntd.0005106. eCollection 2016 Nov.

### **A Cluster-Randomized Controlled Trial to Reduce Diarrheal Disease and Dengue Entomological Risk Factors in Rural Primary Schools in Colombia.**

[Overgaard HJ](#)<sup>1,2,3</sup>, [Alexander N](#)<sup>4</sup>, [Matiz MI](#)<sup>5</sup>, [Jaramillo JF](#)<sup>5</sup>, [Olano VA](#)<sup>5</sup>, [Vargas S](#)<sup>5</sup>, [Sarmiento D](#)<sup>5</sup>, [Lenhart A](#)<sup>6,7</sup>, [Stenström TA](#)<sup>8</sup>.

#### **BACKGROUND:**

As many neglected tropical diseases are co-endemic and have common risk factors, integrated control can efficiently reduce disease burden and relieve resource-strained public health budgets. Diarrheal diseases and dengue fever are major global health problems sharing common risk factors in water storage containers. Where provision of clean water is inadequate, water storage is crucial. Fecal contamination of stored water is a common source of diarrheal illness, but stored water also provides breeding sites for dengue vector mosquitoes. **Integrating improved water management and educational strategies for both diseases in the school environment can potentially improve the health situation for students and the larger community.** The objective of this trial was to investigate whether interventions targeting diarrhea and dengue risk factors would significantly reduce absence due to diarrheal disease and dengue entomological risk factors in schools.

#### **METHODOLOGY/PRINCIPAL FINDINGS:**

A factorial cluster randomized controlled trial was carried out in 34 rural primary schools (1,301 pupils) in La Mesa and Anapoima municipalities, Cundinamarca, Colombia. **Schools were randomized to one of four study arms: diarrhea interventions (DIA), dengue interventions (DEN), combined diarrhea and dengue interventions (DIADEN), and control (CON).** Interventions had no apparent effect on pupil school absence due to diarrheal disease ( $p = 0.45$ ) or on adult female *Aedes aegypti* density ( $p = 0.32$ ) (primary outcomes). However, the dengue interventions reduced the Breteau Index on average by 78% ( $p = 0.029$ ), with Breteau indices of 10.8 and 6.2 in the DEN and DIADEN arms, respectively compared to 37.5 and 46.9 in the DIA and CON arms, respectively. The diarrhea interventions improved water quality as assessed by the amount of *Escherichia coli* colony forming units (CFU); the ratio of Williams mean *E. coli* CFU being 0.22, or 78% reduction ( $p = 0.008$ ).

#### **CONCLUSIONS/SIGNIFICANCE:**

Integrated control of dengue and diarrhea has never been conducted before. **This trial presents an example for application of control strategies that may affect both diseases and the first study to apply such an approach in school settings.** The interventions were well received and highly appreciated by students and teachers. An apparent absence of effect in primary outcome indicators could be the result of pupils being exposed to risk factors outside the school area and mosquitoes flying in from nearby uncontrolled breeding sites. Integrated interventions targeting these diseases in a school context remain promising because of the reduced mosquito breeding and improved water quality, as well as educational benefits. However, **to improve outcomes in future integrated approaches, simultaneous interventions in communities, in addition to**

**schools, should be considered;** using appropriate combinations of site-specific, effective, acceptable, and affordable interventions.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5098800/>

## **Development, cerebral palsy and mental health**

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

[J Nutr.](#) 2017 Feb;147(2):256-263. doi: 10.3945/jn.116.240861. Epub 2016 Dec 28.

[\*\*Large-Scale Behavior-Change Initiative for Infant and Young Child Feeding Advanced Language and Motor Development in a Cluster-Randomized Program Evaluation in Bangladesh.\*\*](#)

### **BACKGROUND:**

Promoting adequate nutrition through interventions to improve infant and young child feeding (IYCF) has the potential to contribute to child development.

### **OBJECTIVE:**

We examined whether an intensive intervention package that was aimed at improving IYCF at scale through the Alive & Thrive initiative in Bangladesh also advanced language and gross motor development, and whether advancements in language and gross motor development were explained through improved complementary feeding.

### **METHODS:**

A cluster-randomized design compared 2 intervention packages: **intensive interpersonal counseling on IYCF, mass media campaign, and community mobilization (intensive) compared with usual nutrition counseling and mass media campaign** (nonintensive).

Twenty subdistricts were randomly assigned to receive either the intensive or the nonintensive intervention. Household surveys were conducted at baseline (2010) and at endline (2014) in the same communities (n = ~ 4000 children aged 0-47.9 mo for each round). Child development was measured by asking mothers if their child had reached each of multiple milestones, with some observed. Linear regression accounting for clustering was used to derive difference-in-differences (DID) impact estimates, and path analysis was used to examine developmental advancement through indicators of improved IYCF and other factors.

### **RESULTS:**

The DID in language development between intensive and nonintensive groups was 1.05 milestones (P = 0.001) among children aged 6-23.9 mo and 0.76 milestones (P = 0.038) among children aged 24-47.9 mo. For gross motor development, the DID was 0.85 milestones (P = 0.035) among children aged 6-23.9 mo. The differences observed corresponded to age- and sex-adjusted effect sizes of 0.35 for language and 0.23 for gross motor development. Developmental advancement at 6-23.9 mo was partially explained through improved minimum dietary diversity and the consumption of iron-rich food.

### **CONCLUSIONS:**

Intensive IYCF intervention differentially advanced language and gross motor development, which was partially explained through improved complementary feeding. Measuring a diverse set of child outcomes, including functional outcomes such as child development, is important when evaluating integrated nutrition programs.

Free access: <http://jn.nutrition.org/content/147/2/256.long>



[J Child Psychol Psychiatry](#). 2016 Dec;57(12):1370-1379. doi: 10.1111/jcpp.12605. Epub 2016 Jul 28.

**Randomized controlled trial of a book-sharing intervention in a deprived South African community: effects on carer-infant interactions, and their relation to infant cognitive and socioemotional outcome.**

[Murray L](#)<sup>1,2,3</sup>, [De Pascalis L](#)<sup>1</sup>, [Tomlinson M](#)<sup>2</sup>, [Vally Z](#)<sup>1</sup>, [Dadomo H](#)<sup>4</sup>, [MacLachlan B](#)<sup>1</sup>, [Woodward C](#)<sup>5</sup>, [Cooper PJ](#)<sup>1,2,3</sup>.

**BACKGROUND:**

Consistent with evidence from high-income countries (HICs), we previously showed that, in an informal peri-urban settlement in a low-middle income country, training parents in book sharing with their infants benefitted infant language and attention (Vally, Murray, Tomlinson, & Cooper, ). Here, we investigated whether these benefits were explained by improvements in carer-infant interactions in both book-sharing and non-book-sharing contexts. We also explored whether infant socioemotional development benefitted from book sharing.

**METHODS:**

We conducted a randomized controlled trial in Khayelitsha, South Africa. **Carers of 14-16-month-old infants were randomized to 8 weeks' training in book sharing (n = 49) or a wait-list control group (n = 42).** In addition to the cognitive measures reported previously, independent assessments were made at base line and follow-up of carer-infant interactions during book sharing and toy play. Assessments were also made, at follow-up only, of infant prosocial behaviour in a 'help task', and of infant imitation of doll characters' nonsocial actions and an interpersonal interaction. Eighty-two carer-infant pairs (90%) were assessed at follow-up. (Trial registration ISRCTN39953901).

**RESULTS:**

Carers who received the training showed significant improvements in book-sharing interactions (sensitivity, elaborations, reciprocity), and, to a smaller extent, in toy-play interactions (sensitivity). **Infants in the intervention group showed a significantly higher rate of prosocial behaviour, and tended to show more frequent imitation of the interpersonal interaction.** Improvements in carer behaviour during book sharing, but not during toy play, mediated intervention effects on all infant cognitive outcomes, and tended to mediate intervention effects on infant interpersonal imitation.

**CONCLUSIONS:**

**Training in book sharing, a simple, inexpensive intervention that has been shown to benefit infant cognitive development in a low-middle income country, also shows promise for improving infant socioemotional outcomes in this context.** Benefits are mediated by improvements in carer-infant interactions, particularly in book-sharing contexts.

[Res Dev Disabil](#). 2016 Sep;56:18-28. doi: 10.1016/j.ridd.2016.05.015. Epub 2016 May 31.

**The effect of parent education program for preschool children with developmental disabilities: A randomized controlled trial.**

[Leung C](#)<sup>1</sup>, [Chan S](#)<sup>2</sup>, [Lam T](#)<sup>3</sup>, [Yau S](#)<sup>3</sup>, [Tsang S](#)<sup>4</sup>.

**AIM:**

This study aimed to evaluate the efficacy of a parent education program, the Happy Parenting program, for Chinese preschool children with developmental disabilities.

**METHODS:**

This study adopted randomized controlled trial design without blinding. Participants were randomized into intervention group (n=62) who were offered the Happy Parenting program delivered by educational psychologists and trainee educational psychologists, and a control group (n=57) who were offered a parent talk after the intervention group had completed

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treatment. Parent participants were requested to complete questionnaires on their children's behavior, their parenting stress, and discipline strategies.

### RESULTS:

Analysis was by intention-to-treat. The results indicated significant decrease in child problem behaviors, parenting stress and dysfunctional discipline strategies in the intervention group at post-intervention.

### CONCLUSION:

This study provided promising evidence on the effectiveness of a parent education program, the Happy Parenting program, for Chinese preschool children with developmental disabilities.

[Dev Neurorehabil.](#) 2017 Apr;20(3):115-120. doi: 10.3109/17518423.2015.1116635. Epub 2016 Feb 18.

### Short-term balance training with computer-based feedback in children with cerebral palsy: A feasibility and pilot randomized trial.

[Saxena S](#)<sup>1</sup>, [Rao BK](#)<sup>2</sup>, [Senthil KD](#)<sup>2</sup>.

### OBJECTIVE:

To assess the feasibility of using short-term balance training with computer-based visual feedback (BTVF) and its effect on standing balance in children with bilateral spastic cerebral palsy (BSCP).

### METHODS:

Out of the fourteen children with BSCP (mean age = 10.31 years), seven children received four sessions of BTVF (two such sessions/day, each session = 15 min) in comparison to the control group that received standard care. Feasibility was measured as percentages of recruitment, retention and safety and balance was measured using a posturography machine as sway velocity (m/s) and velocity moment (m/s<sup>2</sup>) during quiet standing.

### RESULTS:

No serious adverse events occurred in either group. There were no differences in the retention percentages and in any clinical outcome measure between both groups.

### CONCLUSION:

Use of BTVF is feasible in children with BSCP but further investigation is required to estimate a dose-effect relationship.

[JMIR Res Protoc.](#) 2017 May 18;6(5):e93. doi: 10.2196/resprot.6846.

### The Effectiveness of a Computer Game-Based Rehabilitation Platform for Children With Cerebral Palsy: Protocol for a Randomized Clinical Trial.

[Kanitkar A](#)<sup>1</sup>, [Szturm T](#)<sup>2</sup>, [Parmar S](#)<sup>3</sup>, [Gandhi DB](#)<sup>4</sup>, [Rempel GR](#)<sup>5</sup>, [Restall G](#)<sup>2</sup>, [Sharma M](#)<sup>6</sup>, [Narayan A](#)<sup>7</sup>, [Pandian J](#)<sup>4</sup>, [Naik N](#)<sup>8</sup>, [Savadatti RR](#)<sup>9</sup>, [Kamate MA](#)<sup>10</sup>.

### BACKGROUND:

It is difficult to engage young children with cerebral palsy (CP) in repetitive, tedious therapy. As such, there is a need for innovative approaches and tools to motivate these children. We developed the low-cost, computer game-based rehabilitation platform CGR that combines fine manipulation and gross movement exercises with attention and planning game activities appropriate for young children with CP.

### OBJECTIVE:

The objective of this study is to provide evidence of the therapeutic value of CGR to improve upper extremity (UE) motor function for children with CP.

### METHODS:

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This randomized controlled, single-blind, clinical trial with an active control arm will be conducted at 4 sites. Children diagnosed with CP between the ages of 4 and 10 years old with moderate UE impairments and fine motor control abnormalities will be recruited.

### RESULTS:

We will test the difference between experimental and control groups using the Quality of Upper Extremity Skills Test (QUEST) and Peabody Developmental Motor Scales, Second Edition (PDMS-2) outcome measures. The parents of the children and the therapist experiences with the interventions and tools will be explored using semi-structured interviews using the qualitative description approach.

### CONCLUSIONS:

This research protocol, if effective, will provide evidence for the therapeutic value and feasibility of CGR in the pediatric rehabilitation of UE function.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5454217/>

[Biomed Pharmacother.](#) 2017 Mar;87:628-635. doi: 10.1016/j.biopha.2017.01.005. Epub 2017 Jan 10.

### [Comparative study of therapeutic response to baclofen vs tolperisone in spasticity.](#)

[Agarwal S](#)<sup>1</sup>, [Patel T](#)<sup>2</sup>, [Shah N](#)<sup>3</sup>, [Patel BM](#)<sup>4</sup>.

### BACKGROUND:

Spasticity from the upper motor neuron syndrome can result from a variety of conditions affecting the cortex or spinal cord. Some of the more common conditions associated with spasticity include spinal cord injury, cerebral palsy, and post-stroke syndrome. In this study we **compared the efficacy and safety of baclofen vs tolperisone in spasticity**. One hundred fifty patients with cerebral palsy or post stroke or spinal cord injury associated spasticity were enrolled in present study. Group I comprised of Seventy-five patients receiving baclofen and group II comprised of 75 patients receiving tolperisone. For efficacy measurement 4 evaluation methods were used, 1) Modified Ashworth Scale for muscle tone, 2) Medical research council scale for muscle strength and 3) Barthel Index for functional outcome 4) Coefficient of efficacy. **In efficacy evaluation, both groups showed significant improvement in muscle tone, muscle strength and functional outcome at week 6** (Group I, 1.55±0.053, 2.79±0.032, 59.31±1.32; Group II, 1.57±0.053, 3.04±0.032, 73±1.32 respectively). In between the group analysis, there was no significant difference in muscle tone improvement in both the groups after 6 weeks (Group I, 1.055±0.053 vs Group II, 1.57±0.053, p>0.05). Group II showed non-significant but greater improvement in muscle strength (Week 6; Group I, 2.79±0.032 vs Group II, 3.04±0.032, p>0.07). Improvement in functional outcomes was greater in group II as compared to group I (Group I, 59.31±1.32 vs Group II, 73±1.32, p<0.05). Overall efficacy coefficient was greater for group II (3.6) as compared to group I (2.3). **Baclofen showed more side effects compared to tolperisone in, asthenia being the most frequent. Tolperisone offers greater improvement in activities of daily living compared to baclofen.** Tolperisone is more tolerable drug as compared to baclofen.

[PLoS Med.](#) 2017 Feb 28;14(2):e1002237. doi: 10.1371/journal.pmed.1002237. eCollection 2017 Feb.

### [Serotonin transporter gene \(SLC6A4\) polymorphism and susceptibility to a home-visiting maternal-infant attachment intervention delivered by community health workers in South Africa: Reanalysis of a randomized controlled trial.](#)

[Morgan B](#)<sup>1,2,3</sup>, [Kumsta R](#)<sup>4</sup>, [Fearon P](#)<sup>5</sup>, [Moser D](#)<sup>4</sup>, [Skeen S](#)<sup>6</sup>, [Cooper P](#)<sup>6,7,8</sup>, [Murray L](#)<sup>6,7,8</sup>, [Moran G](#)<sup>9</sup>, [Tomlinson M](#)<sup>2,6</sup>.

### BACKGROUND:

Clear recognition of the damaging effects of poverty on early childhood development has fueled an interest in interventions aimed at mitigating these harmful consequences. Psychosocial interventions aimed at alleviating the negative impacts of poverty on children are frequently shown to be of benefit, but effect sizes are typically small to moderate. However, averaging outcomes over an entire sample, as is typically done, could underestimate efficacy because weaker effects on less susceptible individuals would dilute estimation of effects on those more disposed to respond. This study investigates whether a genetic polymorphism of the serotonin transporter gene moderates susceptibility to a psychosocial intervention.

### METHODS AND FINDINGS:

We reanalyzed data from a randomized controlled trial of a home-visiting program delivered by community health workers in a black, isiXhosa-speaking population in Khayelitsha, South Africa. The intervention, designed to enhance maternal-infant attachment, began in the third trimester and continued until 6 mo postpartum. Implemented between April 1999 and February 2003, **the intervention comprised 16 home visits delivered to 220 mother-infant dyads by specially trained community health workers.** A control group of 229 mother-infant dyads did not receive the intervention. Security of maternal-infant attachment was the main outcome measured at infant age 18 mo. **Compared to controls, infants in the intervention group were significantly more likely to be securely attached to their primary caregiver** (odds ratio [OR] = 1.7,  $p = 0.029$ , 95% CI [1.06, 2.76],  $d = 0.29$ ). After the trial, 162 intervention and 172 control group children were reenrolled in a follow-up study at 13 y of age (December 2012-June 2014). At this time, DNA collected from 279 children (134 intervention and 145 control) was genotyped for a common serotonin transporter polymorphism. There were both genetic data and attachment security data for 220 children (110 intervention and 110 control), of whom 40% (44 intervention and 45 control) carried at least one short allele of the serotonin transporter gene. For these 220 individuals, carrying at least one short allele of the serotonin transporter gene was associated with a 26% higher rate of attachment security relative to controls (OR = 3.86,  $p = 0.008$ , 95% CI [1.42, 10.51],  $d = 0.75$ ), whereas there was a negligible (1%) difference in security between intervention and control group individuals carrying only the long allele (OR = 0.95,  $p = 0.89$ , 95% CI [0.45, 2.01],  $d = 0.03$ ). Expressed in terms of absolute risk, for those with the short allele, the probability of secure attachment being observed in the intervention group was 84% (95% CI [73%, 95%]), compared to 58% (95% CI [43%, 72%]) in the control group. For those with two copies of the long allele, 70% (95% CI [59%, 81%]) were secure in the intervention group, compared to 71% (95% CI [60%, 82%]) of infants in the control group. Controlling for sex, maternal genotype, and indices of socioeconomic adversity (housing, employment, education, electricity, water) did not change these results. A limitation of this study is that we were only able to reenroll 49% of the original sample randomized to the intervention and control conditions. Attribution of the primary outcome to causal effects of intervention in the present subsample should therefore be treated with caution.

### CONCLUSIONS:

When infant genotype for serotonin transporter polymorphism was taken into account, the effect size of a maternal-infant attachment intervention targeting impoverished pregnant women increased more than 2.5-fold when only short allele carriers were considered (from  $d = 0.29$  for all individuals irrespective of genotype to  $d = 0.75$ ) and decreased 10-fold when only those carrying two copies of the long allele were considered (from  $d = 0.29$  for all individuals to  $d = 0.03$ ). **Genetic differential susceptibility means that averaging across all participants is a misleading index of efficacy.** The study raises questions about how policy-makers deal with the challenge of balancing equity (equal treatment for all) and efficacy (treating only those whose genes render them likely to benefit) when implementing psychosocial interventions.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5330451/>

### Comment

*It is an unusual way to explain or analyse the results of an RCT, especially for a community-based psychological intervention designed to improve mother-infant attachment; what seems like a universal requirement. The analogy with drug therapies which may be more or less effective in people with certain genetic polymorphisms is well established, especially in cancer treatment, but increasing in the literature with evidence that this applies to some extent in the treatment of tuberculosis and malaria.*

[Prev Sci](#). 2017 Jan;18(1):95-105. doi: 10.1007/s11121-016-0733-5.

### **Parent Training Programs for Ethnic Minorities: a Meta-analysis of Adaptations and Effect.**

[van Mourik K](#)<sup>1</sup>, [Crone MR](#)<sup>2</sup>, [de Wolff MS](#)<sup>3</sup>, [Reis R](#)<sup>2,4,5</sup>.

#### **Abstract**

This meta-analysis focuses on **parent training programs for ethnic minority families** and reports on (i) the adaptation of program content and (ii) the process that informs these adaptations. Relevant studies are reviewed to determine the adaptations made and the impact of the adaptations on parenting and child outcomes. Studies were eligible for inclusion if they enrolled predominantly ethnic minority parents with children aged 0-12 years, used a randomized controlled trial design with post-intervention assessments, focused on group-based parent training programs and on prevention of parenting problems, and reported parenting behavior outcomes. A total of 18 studies were included in the analysis. **The results show that parent training programs targeting ethnic minority parents have a small but significant effect on improving parenting behavior (k = 18, Cohen's d = 0.30), child outcomes (k = 16, Cohen's d = 0.13), and parental perspectives (k = 8, Cohen's d = 0.19).** Most of the programs made adaptations related to surface and deep structure sensitivity. **Programs with cultural adaptations, especially deep structure sensitivity (k = 7, Cohen's d = 0.54), are more effective in improving parenting behavior.** Because only a third of the included studies provided details on the processes that guided the adaptations made, additional studies are needed to provide information on the process of adaptation; this will enable others to learn from the procedures that can be undertaken to culturally adapt interventions.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5236066/>

## Diarrhoea

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

[Indian Pediatr](#). 2016 Jul 8;53(7):595-600.

### **Racecadotril in the Management of Rotavirus and Non-rotavirus Diarrhea in Under-five Children: Two Randomized, Double-blind, Placebo-controlled Trials.**

[Kang G](#)<sup>1</sup>, [Thuppal SV](#), [Srinivasan R](#), [Sarkar R](#), [Subashini B](#), [Venugopal S](#), [Sindhu K](#), [Anbu D](#), [Parez N](#), [Svensson L](#), [Bose A](#).

#### **OBJECTIVE:**



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To study the effect of racecadotril on reduction in the duration of acute rotavirus and non-rotavirus diarrhea.

### DESIGN:

Two randomized double-blind placebo-controlled trials.

### SETTING:

Community-based trial in an urban area in Vellore, hospital-based trial at a secondary hospital in Vellore.

### PARTICIPANTS:

199 and 130 3-59 month old children in the community- and hospital-based trials, respectively.

### METHODS:

Racecadotril (1.5 mg/kg/dose, thrice a day for three days) or placebo were given to manage acute diarrhea in both trials.

### MAIN OUTCOME MEASURE:

Median duration of diarrhea.

### RESULTS:

Among 124 children completing the hospital trial, the median duration of diarrhea was 25 h in both arms ( $P=0.5$ ); median total stool weight was 74 g/kg and 53.5 g/kg in racecadotril group and placebo group, respectively ( $P=0.4$ ); and average fluid intake per day was 3.6 mL/kg/h and 3 mL/kg/h in racecadotril and placebo arms, respectively ( $P=0.3$ ). Among rotavirus-positive children, median duration of diarrhea was 26.9 h and 30.2 h in racecadotril and placebo arms, respectively ( $P=0.7$ ). In the community, 196 completed the trial, the median duration of diarrhea was 2 days for both arms ( $P=0.8$ ) and rotavirus positive children had similar outcomes with median diarrheal duration of 3 d in both arms ( $P=0.4$ ).

### CONCLUSIONS:

**Treatment with racecadotril did not reduce diarrheal duration, stool volume or the requirement for fluid replacement in children with acute gastroenteritis, both with and without rotavirus infection.**

Free access: <https://www.indianpediatrics.net/july2016/595.pdf>

### Comment

*Racecadotril (acetorphan) is an enkephalinase inhibitor that may decrease intestinal hypersecretion but not motility. There is an evidence summary of racecadotril in the NICE Guidelines: <https://www.nice.org.uk/advice/esnm12/chapter/Overview>. In the above study in India, racecadotril was ineffective.*

[J Trop Pediatr.](#) 2016 Dec;62(6):464-470. Epub 2016 Jun 9.

### Efficacy and Safety of Saccharomyces boulardii in Acute Rotavirus Diarrhea: Double Blind Randomized Controlled Trial from a Developing Country.

[Das S](#)<sup>1</sup>, [Gupta PK](#)<sup>2</sup>, [Das RR](#)<sup>3</sup>.

### OBJECTIVE:

To study the efficacy and safety of Saccharomyces boulardii (SB) in acute childhood rotavirus diarrhea.

### METHODS:

Children (3 months to 5 years) with WHO-defined acute watery diarrhea and stool rotavirus positive ( $n = 60$ ) were randomized into intervention ( $n = 30$ ) and control ( $n = 30$ ) groups. The intervention group received SB (500 mg/day) for 5 days.

### RESULTS:

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The median duration (hours) of diarrhea was significantly shorter in the intervention group (60 vs. 89; 95% CI: -41.2 to -16.8). A significantly shorter duration of hospitalization (74 vs. 91; 95% CI: -33.46 to -0.54) was also seen in the intervention group, but no significant difference was seen for fever and vomiting. There was also no difference between the two groups in the proportion of children requiring parenteral rehydration and persistence of diarrhea lasting beyond day 7. There was no report of any adverse events.

### CONCLUSIONS:

The present trial showed that SB is effective and safe in acute rotavirus diarrhea.

### Comment

*Saccharomyces boulardii* has probiotic effects. A Cochrane review of 63 RCTs showed an overall benefit of probiotics on acute infectious diarrhoea in children

([http://www.cochrane.org/CD003048/INFECTN\\_probiotics-for-treating-acute-infectious-diarrhoea](http://www.cochrane.org/CD003048/INFECTN_probiotics-for-treating-acute-infectious-diarrhoea)) and a Child Health Epidemiology Reference Group also published a meta-analysis: <https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-S3-S16>

## Cholera

PLoS Med. 2016 Sep 13;13(9):e1002120. doi: 10.1371/journal.pmed.1002120. eCollection 2016 Sep.

### Potential for Controlling Cholera Using a Ring Vaccination Strategy: Re-analysis of Data from a Cluster-Randomized Clinical Trial.

Ali M<sup>1</sup>, Debes AK<sup>1</sup>, Luquero FJ<sup>1</sup>, Kim DR<sup>2</sup>, Park JY<sup>2</sup>, Digilio L<sup>2</sup>, Manna B<sup>3</sup>, Kanungo S<sup>3</sup>, Dutta S<sup>3</sup>, Sur D<sup>3</sup>, Bhattacharya SK<sup>3</sup>, Sack DA<sup>1</sup>.

### INTRODUCTION:

Vaccinating a buffer of individuals around a case (ring vaccination) has the potential to target those who are at highest risk of infection, reducing the number of doses needed to control a disease. We explored the potential vaccine effectiveness (VE) of oral cholera vaccines (OCVs) for such a strategy.

### METHODS AND FINDINGS:

This analysis uses existing data from a cluster-randomized clinical trial in which OCV or placebo was given to 71,900 participants in Kolkata, India, from 27 July to 10 September 2006. Cholera surveillance was then conducted on 144,106 individuals living in the study area, including trial participants, for 5 y following vaccination. First, we explored the risk of cholera among contacts of cholera patients, and, second, we measured VE among individuals living within 25 m of cholera cases between 8 and 28 d after onset of the index case. For the first analysis, individuals living around each index case identified during the 5-y period were assembled using a ring to define cohorts of individuals exposed to cholera index cases. An index control without cholera was randomly selected for each index case from the same population, matched by age group, and individuals living around each index control were assembled using a ring to define cohorts not exposed to cholera cases. Cholera attack rates among the exposed and non-exposed cohorts were compared using different distances from the index case/control to define the rings and different time frames to define the period at risk. For the VE analysis, the exposed cohorts were further stratified according to the level of vaccine coverage into high and low coverage strata. Overall VE was assessed by comparing the attack rates between high and low vaccine coverage strata irrespective of individuals' vaccination status, and indirect VE was assessed by comparing the attack rates among unvaccinated members between high and low vaccine coverage strata. **Cholera risk among the cohort exposed to cholera cases was 5-11 times higher than that among the cohort not exposed to cholera cases.** The risk gradually

diminished with an increase in distance and time. The overall and indirect VE measured between 8 and 28 d after exposure to a cholera index case during the first 2 y was 91% (95% CI 62%-98%) and 93% (95% CI 44%-99%), respectively. VE persisted for 5 y after vaccination and was similar whether the index case was a young child (<5 y) or was older. Of note, this study was a reanalysis of a cholera vaccine trial that used two doses; thus, a limitation of the study relates to the assumption that a single dose, if administered quickly, will induce a similar level of total and indirect protection over the short term as did two doses.

### CONCLUSIONS:

These findings suggest that **high-level protection can be achieved if individuals living close to cholera cases are living in a high coverage ring**. Since this was an observational study including participants who had received two doses of vaccine (or placebo) in the clinical trial, further studies are needed to determine whether a ring vaccination strategy, in which vaccine is given quickly to those living close to a case, is feasible and effective.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5021260/>

[Am J Trop Med Hyg.](#) 2016 Dec 7;95(6):1292-1298. Epub 2016 Oct 10.

### Promotion of Cholera Awareness Among Households of Cholera Patients: A Randomized Controlled Trial of the Cholera-Hospital-Based-Intervention-for-7 Days (CHoBI7) Intervention.

[Saif-Ur-Rahman KM<sup>1</sup>](#), [Parvin T<sup>1</sup>](#), [Bhuyian SI<sup>1</sup>](#), [Zohura F<sup>1</sup>](#), [Begum F<sup>1</sup>](#), [Rashid MU<sup>1</sup>](#), [Biswas SK<sup>1</sup>](#), [Sack D<sup>2</sup>](#), [Sack RB<sup>2</sup>](#), [Monira S<sup>1</sup>](#), [Alam M<sup>1</sup>](#), [Shaly NJ<sup>1</sup>](#), [George CM<sup>3</sup>](#).

#### Abstract

Previous studies have demonstrated that household contacts of cholera patients are highly susceptible to cholera infections for a 7-day period after the presentation of the index patient in the hospital. However, there is no standard of care to prevent cholera transmission in this high-risk population. Furthermore, there is limited information available on awareness of cholera transmission and prevention among cholera patients and their household contacts. To initiate a standard of care for this high-risk population, we developed the Cholera-Hospital-Based-Intervention-for-7-Days (CHoBI7), which delivers a handwashing with soap and water treatment intervention to household contacts during the time they spend with the admitted cholera patient in the hospital and reinforces these messages through home visits. To test CHoBI7, we conducted a randomized controlled trial among **302 intervention cholera patient household members and 302 control cholera patient household members in Dhaka, Bangladesh**. In this study, we evaluated the effectiveness of the CHoBI7 intervention in increasing awareness of cholera transmission and prevention, and the key times for handwashing with soap. **We observed a significant increase in cholera knowledge score in the intervention arm compared with the control arm at both the 1-week follow-up {score coefficient = 2.34 (95% confidence interval [CI] = 1.96, 2.71)} and 6 to 12-month follow-up period (score coefficient = 1.59 [95% CI = 1.05, 2.13])**. This 1-week hospital- and home-based intervention led to a significant increase in knowledge of cholera transmission and prevention which was sustained 6 to 12 months post-intervention. These findings suggest that the CHoBI7 intervention presents a promising approach to increase cholera awareness among this high-risk population.

Water quality and purification



[Am J Trop Med Hyg.](#) 2016 Jul 6;95(1):239-46. doi: 10.4269/ajtmh.15-0854. Epub 2016 May 23.

**Subsidized Sachet Water to Reduce Diarrheal Disease in Young Children: A Feasibility Study in Accra, Ghana.**

[Wright J](#)<sup>1</sup>, [Dzodzomenyo M](#)<sup>2</sup>, [Fink G](#)<sup>3</sup>, [Wardrop NA](#)<sup>4</sup>, [Aryeetey GC](#)<sup>2</sup>, [Adanu RM](#)<sup>2</sup>, [Hill AG](#)<sup>5</sup>.

**Abstract**

Use of drinking water sold in plastic bags (sachet water) is growing rapidly in west Africa. The impact on water consumption and child health remains unclear, and a debate on the taxation and regulation of sachet water is ongoing. This study assessed the feasibility of providing subsidized sachet water to low-income urban households in Accra and measured the resultant changes in water consumption. **A total of 86 children, 6-36 months of age in neighborhoods lacking indoor piped water, were randomized to three study arms. The control group received education about diarrhea. The second arm received vouchers for 15 L/week/child of free water sachets (value: \$0.63/week) plus education. The third arm received vouchers for the same water sachet volume at half price plus education.** Water consumption was measured at baseline and followed for 4 months thereafter. At baseline, 66 of 81 children (82%) drank only sachet water. When given one voucher/child/week, households redeemed an average 0.94 vouchers/week/child in the free-sachet-voucher arm and 0.82 vouchers/week/child in the half-price arm. No change in water consumption was observed in the half-price arm, although the study was not powered to detect such differences. In the free-sachet-voucher arm, estimated sachet water consumption increased by 0.27 L/child/day (P = 0.03). **The increase in sachet water consumption by children in the free-sachet-voucher arm shows that provision of fully subsidized water sachets might improve the quality of drinking water consumed by children.** Further research is needed to quantify this and any related child health impacts.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944696/>

## Ebola and viral haemorrhagic fever

[N Engl J Med.](#) 2016 Oct 13;375(15):1448-1456.

**A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection.**

[PREVAIL II Writing Group](#); [Multi-National PREVAIL II Study Team](#), [Davey RT Jr](#), [Dodd L](#), [Proschan MA](#), [Neaton J](#), [Neuhaus Nordwall J](#), [Koopmeiners JS](#), [Beigel J](#), [Tierney J](#), [Lane HC](#), [Fauci AS](#), [Massaquoi MBF](#), [Sahr F](#), [Malvy D](#).

**Abstract**

**BACKGROUND:**

Data from studies in nonhuman primates suggest that the triple monoclonal antibody cocktail ZMapp is a promising immune-based treatment for Ebola virus disease (EVD).

**METHODS:**

Beginning in March 2015, we conducted a randomized, controlled trial of **ZMapp plus the current standard of care as compared with the current standard of care alone in patients with EVD that was diagnosed in West Africa by polymerase-chain-reaction (PCR) assay.** Eligible patients of any age were randomly assigned in a 1:1 ratio to receive either the current standard of care or the current standard of care plus three intravenous infusions of ZMapp (50 mg per kilogram of body weight, administered every third day). Patients were stratified according to baseline PCR cycle-threshold value for the virus ( $\leq 22$  vs.  $> 22$ ) and country of enrollment. Oral favipiravir was part of the current standard of care in Guinea. The primary end point was mortality at 28 days.

**RESULTS:**

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A total of 72 patients were enrolled at sites in Liberia, Sierra Leone, Guinea, and the United States. Of the 71 patients who could be evaluated, 21 died, representing an overall case fatality rate of 30%. **Death occurred in 13 of 35 patients (37%) who received the current standard of care alone and in 8 of 36 patients (22%) who received the current standard of care plus ZMapp.** The observed posterior probability that ZMapp plus the current standard of care was superior to the current standard of care alone was 91.2%, falling short of the prespecified threshold of 97.5%. Frequentist analyses yielded similar results (absolute difference in mortality with ZMapp, -15 percentage points; 95% confidence interval, -36 to 7). Baseline viral load was strongly predictive of both mortality and duration of hospitalization in all age groups.

### CONCLUSIONS:

**In this randomized, controlled trial of a putative therapeutic agent for EVD, although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the prespecified statistical threshold for efficacy.** (Funded by the National Institute of Allergy and Infectious Diseases and others; PREVAIL II ClinicalTrials.gov number, [NCT02363322](https://clinicaltrials.gov/ct2/show/study/NCT02363322) ).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5086427/>

### Comment

*ZMapp is a combination of 3 monoclonal antibodies that bind to the surface glycoprotein of Ebola virus. The three monoclonal antibodies, called c13C6, c2G4, and c4G7, were produced by immunizing mice with a vesicular stomatitis virus in which the glycoprotein was replaced with that from Ebola virus. Antibodies that bound the viral glycoprotein and protected mice from infection were identified, and the three antibodies were made to resemble human antibodies and produced in tobacco plants.*

## Endocrine disorders and bone health

[J Bone Miner Res.](#) 2016 Nov;31(11):2024-2031. doi: 10.1002/jbmr.2886. Epub 2016 Sep 7.  
**[Optimal Dose of Calcium for Treatment of Nutritional Rickets: A Randomized Controlled Trial.](#)**

### Abstract

Calcium supplementation is indicated for the treatment of nutritional rickets. Our aim was to determine the optimal dose of calcium for treatment of children with rickets. **Sixty-five Nigerian children with radiographically confirmed rickets were randomized to daily supplemental calcium intake of 500 mg (n = 21), 1000 mg (n = 23), or 2000 mg (n = 21).** Venous blood, radiographs, and forearm areal bone density (aBMD) were obtained at baseline and at 8, 16, and 24 weeks after enrollment. The primary outcome was radiographic healing, using a 10-point radiographic severity score. **The radiographic severity scores improved in all three groups, but the rate of radiographic healing (points per month) was significantly more rapid in the 1000-mg (-0.29; 95% confidence interval [CI] -0.13 to -0.45) and 2000-mg (-0.36; 95% CI -0.19 to -0.53) supplementation groups relative to the 500-mg group.** The 2000-mg group did not heal more rapidly than the 1000-mg group. Of those who completed treatment for 24 weeks, 12 (67%), 20 (87%), and 14 (67%) in the 2000-mg, 1000-mg, and 500-mg groups, respectively, had achieved a radiographic score of 1.5 or less (p = 0.21). Serum alkaline phosphatase decreased and calcium increased similarly in all groups. Forearm diaphyseal aBMD improved significantly more rapidly in the 2000-mg group than in the 500-mg and 1000-mg groups (p < 0.001). **Daily calcium intakes of 1000 mg or 2000 mg produced**

**more rapid radiographic healing of rickets than 500 mg**, but 2000 mg did not have greater benefit than 1000 mg. Some children require longer than 24 weeks for complete healing of nutritional rickets.

[BMC Endocr Disord.](#) 2016 Nov 26;16(1):67.

**A randomised, open-label study of insulin glargine or neutral protamine Hagedorn insulin in Chinese paediatric patients with type 1 diabetes mellitus.**

[Liu M](#)<sup>1</sup>, [Zhou Z](#)<sup>2</sup>, [Yan J](#)<sup>3</sup>, [Li P](#)<sup>4</sup>, [Song W](#)<sup>5</sup>, [Fu J](#)<sup>6</sup>, [Chen X](#)<sup>7</sup>, [Zhao W](#)<sup>8</sup>, [Xi L](#)<sup>9</sup>, [Luo X](#)<sup>10</sup>, [Sha L](#)<sup>11</sup>, [Deng X](#)<sup>11</sup>, [Gong C](#)<sup>12</sup>.

**Abstract**

**BACKGROUND:**

We aimed to describe the safety and efficacy of insulin glargine in Chinese paediatric patients with type 1 diabetes mellitus (T1DM). Neutral protamine Hagedorn (NPH) insulin was the reference therapy.

**METHODS:**

This open-label, randomised, Phase III study was conducted at 10 sites in China. Children aged  $\geq 6$  to  $< 18$  years with T1DM were randomised (2:1) to insulin glargine or NPH insulin as basal insulin for a 24-week treatment period. For all patients, insulin aspart was given as bolus insulin. The primary endpoint was absolute change in glycated haemoglobin (HbA1c) from baseline to Week 24. Secondary endpoints included the percentage of patients reaching HbA1c  $< 7.5\%$  ( $< 58.5$  mmol/mol), and safety. The study was registered at clinicaltrials.gov ([NCT01223131](#)).

**RESULTS:**

In total, 196 patients were screened, and 162 were randomised (107 and 55 patients were randomised to insulin glargine and NPH insulin, respectively). The mean  $\pm$  SD of absolute change in HbA1c was  $-0.25 \pm 1.68\%$  ( $-2.69 \pm 18.32$  mmol/mol) in the insulin glargine group and  $-0.54 \pm 1.67\%$  ( $-5.55 \pm 20.32$  mmol/mol) in the NPH insulin group. At Week 24, 18.7 and 21.6% of patients in the insulin glargine and NPH insulin groups achieved HbA1c  $< 7.5\%$  ( $< 58.5$  mmol/mol). Both treatments were generally well tolerated. A numerically lower rate of symptomatic hypoglycaemia per patient year was observed for insulin glargine versus NPH insulin ( $24.3 \pm 45.8$  versus  $32.3 \pm 43.2$ ); severe hypoglycaemia was rare ( $< 2\%$ ).

**CONCLUSIONS:**

Initiation of insulin glargine can aid Chinese paediatric patients with T1DM to safely reduce their HbA1c levels.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5124261/>

## Enterovirus infections

## Envenomation and toxins

[Syst Rev.](#) 2017 Apr 8;6(1):74. doi: 10.1186/s13643-017-0469-8.

**Management of scorpion envenoming: a systematic review and meta-analysis of controlled clinical trials.**

[Rodrigo C](#)<sup>1</sup>, [Gnanathanan A](#)<sup>2</sup>.

**Abstract**

**BACKGROUND:**

Scorpion stings cause an estimated 3000 deaths per annum worldwide. We conducted a systematic review of all controlled clinical trials related to scorpion sting management.

### METHODS:

We searched PubMed, EMBASE, Scopus, Web of Science and CINAHL and included controlled prospective clinical trials (randomized or non-randomized). The following interventions were assessed: adults and children with scorpion stings treated with (a) steroids vs. placebo, (b) different methods of pain relief, (c) antivenom vs. supportive treatment, (d) prazosin vs. supportive treatment, (e) antivenom vs. prazosin and (f) antivenom plus prazosin vs. prazosin alone. When trials had comparative outcomes, they were combined in a meta-analysis. Data was analysed with Review Manager 5. Dichotomous data were compared with relative risk (RR), and continuous data were compared with mean differences using a fixed effect model. There is no PROSPERO registration number for this study.

### RESULTS:

Antivenom against *Centruroides* sp. are effective in reversing the clinical syndrome faster than no antivenom treatment in children (RR, 0.02; 95% CI, 0.01 to 0.06; 322 participants; three trials). Antivenom (against *Mesobuthus tamulus*) and prazosin combination is better than prazosin alone for faster resolution of symptoms (mean difference, -12.59 h; 95% CI, -14.01 to -11.17; 173 participants; three trials).

### CONCLUSIONS:

**The polyvalent antivenom against *Centruroides* sp. in USA/Mexico and the monovalent antivenom against *M. tamulus* in India are effective for rapid resolution of symptoms. Prazosin is useful as an add-on therapy for *M. tamulus* stings.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5385045/>

Toxicon. 2016 Sep 15;120:159-65. doi: 10.1016/j.toxicon.2016.08.011. Epub 2016 Aug 13.

**Efficacy of intravenous hydrocortisone administered 2-4 h prior to antivenom as prophylaxis against adverse drug reactions to snake antivenom in Sri Lanka: An open labelled randomized controlled trial.**

Kularatne SA<sup>1</sup>, Weerakoon K<sup>2</sup>, Silva A<sup>3</sup>, Maduwage K<sup>4</sup>, Walathara C<sup>5</sup>, Rathnayake I<sup>5</sup>, Medagedara S<sup>1</sup>, Paranagama R<sup>5</sup>, Mendis S<sup>5</sup>, Kumarasiri PV<sup>6</sup>.

### Abstract

The prevention of adverse drug reactions to antivenom serum poses a formidable challenge in the management of snakebite. **Hydrocortisone is being used concurrently with antivenom in order to prevent these adverse drug reactions without a proven benefit.** However, all previous studies seemed to ignore the testing of effectiveness of hydrocortisone therapy during its pharmacological effects, which come hours later. On this principle, we aimed to test the effectiveness of intravenous hydrocortisone given 2 h or more prior to the commencement of antivenom therapy to reduce adverse drug reactions to antivenom. In an open-labelled randomized controlled trial, **patients with a history of snakebite were randomly assigned to receive either 500 mg intravenous hydrocortisone bolus given 2 h or more prior to antivenom therapy (Group A) or at the time of antivenom therapy (Group B).** The primary endpoint was the reduction of adverse drug reactions to antivenom of any grade of severity within the first 48 h. This trial has been registered with the "Sri Lanka Clinical Trials Registry", number SLCTR/2010/005. A total of 236 patients were randomized to group A or Group B. **In the group A, 38 participants received hydrocortisone 2 h before administration of antivenom whilst 33 received hydrocortisone less than 2 h before administration of antivenom.** In the Group B, 84 participants received hydrocortisone at the time of antivenom therapy. In Group A (n, 38), and Group B (n, 84), 15 patients (39%) and 29 patients (35%) developed reactions respectively and the difference is not significant (p = 0.598). **Moreover, hydrocortisone therapy did not significantly reduce the occurrence of antivenom reactions**

**of any grade of severity.** Further, it didn't delay the occurrence of antivenom reactions in patients who received hydrocortisone either more than 2 h or less than 2 h before the antivenom as opposed to the control group (group B). **Intravenous hydrocortisone shows no difference in the timing, rate or severity of adverse drug reactions to antivenom when administered simultaneously and up to 4 h prior to antivenom.**

## **Epilepsy and acute seizures**

[Int J Neurosci.](#) 2016 Nov;126(11):1013-9. doi: 10.3109/00207454.2015.1095743. Epub 2015 Oct 20.

[A comparison of four antiepileptic drugs in status epilepticus: experience from India.](#)  
[Misra UK<sup>1</sup>, Kalita J<sup>1</sup>.](#)

### **PURPOSE:**

We report the efficacy and safety of lorazepam (LOR), phenytoin (PHT), valproate (VPA) and levetiracetam (LEV) as first and second choice antiepileptic drug (AED) in status epilepticus (SE) and their combinations in preventing refractory SE.

### **MATERIALS AND METHODS:**

The results of our two earlier trials on SE were compared; one evaluated VPA versus PHT (group I) and the other LOR versus LEV (group II). In group I, additional patients were recruited in addition to published data. The primary outcome was cessation of SE after first and second AEDs and secondary outcome was mortality and side effects. The efficacy of these four drugs as first and second choice was compared. The frequency of refractory seizure in groups I and II and their contributing factors were analyzed.

### **RESULTS:**

One hundred and seventeen patients were in group I and 79 in group II. The baseline characteristics of the patients were similar in LOR, LEV, VPA and PHT groups. As a first choice, **LOR controlled SE in 75.1%, LEV in 76.3%, VPA in 55.4% and PHT in 44.2% patients. As a second choice, LEV was effective in 88.9%, LOR in 70%, VPA in 74.1% and PHT in 25% patients.** Refractory SE was more frequent in group I than group II (29.9% versus 10.5%), however, complications and mortality were higher in group II.

### **CONCLUSION:**

LOR and LEV combination was superior in reducing refractory SE but at the cost of higher complications and death.

[Epilepsy Res.](#) 2016 Nov;127:152-159. doi: 10.1016/j.epilepsyres.2016.09.002. Epub 2016 Sep 1.

[Evaluation of a simplified modified Atkins diet for use by parents with low levels of literacy in children with refractory epilepsy: A randomized controlled trial.](#)

[Sharma S<sup>1</sup>, Goel S<sup>2</sup>, Jain P<sup>3</sup>, Agarwala A<sup>4</sup>, Aneja S<sup>5</sup>.](#)

### **Author information**

### **PURPOSE:**

This study was planned to develop and evaluate a simple, easy-to-understand variation of the modified Atkins diet, for use by parents with low levels of literacy in children with refractory epilepsy.

### **METHODS:**

This study was conducted in two phases. In the first phase, a simplified version of the modified Atkins diet was developed. In the second phase this was evaluated in children aged 2-14 years who had daily seizures despite the appropriate use of at least two anticonvulsant drugs, in an



open-label randomized-controlled-trial. **Children were randomized to receive either the simplified modified Atkins diet or no dietary intervention for a period of 3 months with the ongoing anticonvulsant medications being continued unchanged in both the groups.** Reduction in seizure frequency was the primary outcome-measure. Data was analyzed using intention to treat approach. Adverse effects were also studied. (Clinical trial identifier [NCT0189989](https://clinicaltrials.gov/ct2/show/study/NCT0189989)).

### RESULTS:

Forty-one children were randomly assigned to the diet-group, and 40 were assigned to the control-group. Two patients discontinued the diet during the study period. **The proportion of children with >50% seizure reduction was significantly higher in the diet group as compared to the control group (56.1% vs 7.5%,  $p < 0.0001$ ).** The proportion of children with 90% seizure reduction was also higher in the diet group (19.5% vs 2%,  $p = 0.09$ ). Six children in the diet group were seizure free at 3 months compared with two in the control group ( $p = 0.26$ ). At 3 months, 6 children had constipation and 5 had weight loss.

### CONCLUSION:

A simplified version of the modified Atkins diet was developed for use by parents with low levels literacy. This diet was found to be feasible, efficacious and well tolerated in children with refractory epilepsy.

### Comment

*The Atkins diet is a modified ketogenic diet, in which butter and vegetable oils provide the necessary high-fat intake. The diet allows all protein rich foods such as meat, chicken, eggs and fish. It completely eliminates refined carbohydrates and sugars: sweets, biscuits and desserts. Some carbohydrates such as bread, potatoes, rice and cereals are not allowed in the first month of the diet, but may be introduced later when there is better seizure control.*

<http://www.epilepsyqueensland.com.au/modified-atkins-diet>;

<http://www.epilepsy.com/learn/treating-seizures-and-epilepsy/dietary-therapies/modified-atkins-diet>

## Hygiene, sanitation and environmental health

(See also Environmental enteropathy)

[Water Res.](#) 2016 Sep 1;100:232-44. doi: 10.1016/j.watres.2016.05.015. Epub 2016 May 4.

### [Human fecal and pathogen exposure pathways in rural Indian villages and the effect of increased latrine coverage.](#)

[Odagiri M](#)<sup>1</sup>, [Schriewer A](#)<sup>1</sup>, [Daniels ME](#)<sup>2</sup>, [Wuertz S](#)<sup>3</sup>, [Smith WA](#)<sup>2</sup>, [Clasen T](#)<sup>4</sup>, [Schmidt WP](#)<sup>5</sup>, [Jin Y](#)<sup>1</sup>, [Torondel B](#)<sup>5</sup>, [Misra PR](#)<sup>6</sup>, [Panigrahi P](#)<sup>7</sup>, [Jenkins MW](#)<sup>8</sup>.

### Abstract

Efforts to eradicate open defecation and improve sanitation access are unlikely to achieve health benefits unless interventions reduce microbial exposures. This study assessed human fecal contamination and pathogen exposures in rural India, and the effect of increased sanitation coverage on contamination and exposure rates. **In a cross-sectional study of 60 villages of a cluster-randomized controlled sanitation trial in Odisha, India, human and domestic animal fecal contamination was measured in community tubewells and ponds (n = 301) and via exposure pathways in homes (n = 354), using Bacteroidales microbial source tracking fecal markers validated in India.** Community water sources were further tested for diarrheal pathogens (rotavirus, adenovirus and *Vibrio cholerae* by quantitative PCR; pathogenic *Escherichia coli* by multiplex PCR; *Cryptosporidium* and *Giardia* by immunomagnetic separation and direct fluorescent antibody microscopy). Exposure pathways in intervention and control villages were

compared and relationships with child diarrhea examined. Human fecal markers were rarely detected in tubewells (2.4%, 95% CI: 0.3-4.5%) and ponds (5.6%, 95% CI: 0.8-10.3%), compared to homes (35.4%, 95% CI: 30.4-40.4%). In tubewells, *V. cholerae* was the most frequently detected pathogen (19.8%, 95% CI: 14.4-25.2%), followed by *Giardia* (14.8%, 95% CI: 10.0-19.7%). In ponds, *Giardia* was most often detected (74.5%, 95% CI: 65.7-83.3%), followed by pathogenic *E. coli* (48.1%, 95% CI: 34.8-61.5%) and rotavirus (44.4%, 95% CI: 34.2-54.7%). **At village-level, prevalence of fecal pathogen detection in community drinking water sources was associated with elevated prevalence of child diarrhea within 6 weeks of testing (RR 2.13, 95% CI: 1.25-3.63) while within homes, higher levels of human and animal fecal marker detection were associated with increased risks of subsequent child diarrhea (P = 0.044 and 0.013, respectively).** There was no evidence that the intervention, which increased functional latrine coverage and use by 27 percentage points, reduced human fecal contamination in any tested pathway, nor the prevalence of pathogens in water sources. **In conclusion, the study demonstrates that (1) improved sanitation alone may be insufficient and further interventions needed in the domestic domain to reduce widespread human and animal fecal contamination observed in homes, (2) pathogens detected in tubewells indicate these sources are microbiologically unsafe for drinking and were associated with child diarrhea, (3) domestic use of ponds heavily contaminated with multiple pathogens presents an under-recognized health risk, and (4) a 27 percentage point increase in improved sanitation access at village-level did not reduce detectable human fecal and pathogen contamination in this setting.**

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Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4907306/>

[J Health Econ.](#) 2016 Jul;48:135-48. doi: 10.1016/j.jhealeco.2016.03.003. Epub 2016 Apr 20.

**Village sanitation and child health: Effects and external validity in a randomized field experiment in rural India.**

[Hammer J<sup>1</sup>](#), [Spears D<sup>2</sup>](#).

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### **Abstract**

Over a billion people worldwide defecate in the open, with important consequences for early-life health and human capital accumulation in developing countries. We report a cluster randomized controlled trial of a village sanitation intervention conducted in rural Maharashtra, India designed to identify an effect of village sanitation on average child height, an outcome of increasing importance to economists. We find an effect of approximately 0.3 height-for-age standard deviations, which is consistent with observations and hypotheses in economic and health literatures. We further exploit details of the planning and implementation of the experiment to study treatment heterogeneity and external validity.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4920645/>



## Haematological disorders

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

[Am J Hematol.](#) 2017 Apr 25. doi: 10.1002/ajh.24770. [Epub ahead of print]

### Feasibility trial for primary stroke prevention in children with sickle cell anemia in Nigeria (SPIN trial).

[Galadanci NA](#)<sup>1</sup>, [Umar Abdullahi S](#)<sup>2</sup>, [Vance LD](#)<sup>3</sup>, [Musa Tabari A](#)<sup>4</sup>, [Ali S](#)<sup>4</sup>, [Belonwu R](#)<sup>2</sup>, [Salihu A](#)<sup>5</sup>, [Amal Galadanci A](#)<sup>1</sup>, [Wudil Jibir B](#)<sup>6</sup>, [Bello-Manga H](#)<sup>7</sup>, [Neville K](#)<sup>8</sup>, [Kirkham FJ](#)<sup>9</sup>, [Shyr Y](#)<sup>10</sup>, [Phillips S](#)<sup>10</sup>, [Covert BV](#)<sup>11</sup>, [Kassim AA](#)<sup>12</sup>, [Jordan LC](#)<sup>11</sup>, [Aliyu MH](#)<sup>13</sup>, [DeBaun MR](#)<sup>11</sup>.

#### Abstract

The vast majority of children with sickle cell anemia (SCA) live in Africa, where evidence-based guidelines for primary stroke prevention are lacking. **In Kano, Nigeria, we conducted a feasibility trial to determine the acceptability of hydroxyurea therapy for primary stroke prevention in children with abnormal transcranial Doppler (TCD) measurements.** Children with SCA and abnormal nonimaging TCD measurements ( $\geq 200$  cm/s) received moderate fixed-dose hydroxyurea therapy (~ 20 mg/kg/day). A comparison group of children with TCD measurements  $< 200$  cm/s was followed prospectively. Approximately 90% (337 of 375) of families agreed to be screened, while 93% (29 of 31) of those with abnormal TCD measurements, enrolled in the trial. No participant elected to withdraw from the trial. The average mean corpuscular volume increased from 85.7 fl at baseline to 95.5 fl at 24 months (not all of the children who crossed over had a 24 month visit). Demonstrating adherence to hydroxyurea. The comparison group consisted of initially 210 children, of which four developed abnormal TCD measurements, and were started on hydroxyurea. None of the monthly research visits were missed ( $n =$  total 603 visits). Two and 10 deaths occurred in the treatment and comparison groups, with mortality rates of 2.69 and 1.81 per 100 patient-years, respectively ( $P = .67$ ). Our results provide strong evidence, for high family recruitment, retention, and adherence rates, to undertake the first randomized controlled trial with hydroxyurea therapy for primary stroke prevention in children with SCA living in Africa.

[Cochrane Database Syst Rev.](#) 2016 Oct 6;10:CD011175.

### Interventions for patients and caregivers to improve knowledge of sickle cell disease and recognition of its related complications.

[Asnani MR](#)<sup>1</sup>, [Quimby KR](#), [Bennett NR](#), [Francis DK](#).

#### Abstract

##### BACKGROUND:

Sickle cell disease is a group of genetic diseases which is especially prevalent in tropical and subtropical regions; however, forced migration and ongoing population movement have spread it throughout the world, with estimated birth rates reaching 0.49 per 1000 in the Americas, 0.07 per 1000 in Europe, 0.68 per 1000 in South and Southeast Asia, and 10.68 per 1000 in Africa. Life for individuals with sickle cell disease can be affected by repeated acute complications and compounded by progressive organ damage. Studies reveal that when people with chronic illness learn self-management, their clinical outcomes and quality of life improves; and they show lower dependence on healthcare services. There are, however, no reviews identifying which interventions improve knowledge and little is known about the impact of patient or care-giver knowledge on clinical and psychosocial outcomes in people with sickle cell disease.

##### OBJECTIVES:

## Randomised trials in child health in developing countries 2016-17

1. To determine the effectiveness of patient- and caregiver-centred educational interventions for changing knowledge and understanding of sickle cell disease among patients as well as caregivers of people with the disease. 2. To assess the effectiveness and safety of patient- and caregiver-centred educational interventions and programs for the recognition of signs and symptoms of disease-related morbidity, adherence to treatment and healthcare utilization in patients with sickle cell disease.

### SEARCH METHODS:

The authors searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. Additional trials were sought from the reference lists of the trials and reviews identified by the search strategy. Date of last search: 11 April 2016.

### SELECTION CRITERIA:

Randomized and quasi-randomized controlled trials which evaluate the effectiveness of individual- and group-based interventions for either the patient with sickle cell disease or their caregivers, or both. Eligible interventions will aim to change knowledge, attitudes or skills, improve psychosocial aspects of the disease as well as treatment adherence and healthcare utilization. Trials evaluating the intervention versus no program, comparing two interventions and those which are part of a multi-faceted intervention to improve a range of sickle cell-related health outcomes are all eligible for inclusion.

### DATA COLLECTION AND ANALYSIS:

Two review authors independently selected trials based on stated inclusion criteria and thereafter examined each selected report to extract data using a prepared, piloted, data collection form. A third author assisted in reaching consensus if there were any discrepancies. Similarly, risk of bias was assessed by two authors and verified by a third author.

### MAIN RESULTS:

A total of 12 trials (11 randomized controlled trials and one quasi-randomized trial) of 563 people with HbSS, HbSC or HbS $\beta$ thal, aged six to 35 years old, were included in the review; the majority of participants were African-American. **Interventions ranged from a total of one hour to weekly sessions for eight weeks and the post-intervention assessments ranged from the end of the intervention period to 12 months after completion.** The heterogeneity of the included trials, which encompasses setting, inclusion and exclusion criteria, interventional method and time of assessment, ranged from 'not important' to 'moderate to substantial' for different review outcomes. The overall risk of bias was low for selective reporting, unclear for random sequence generation, allocation concealment, blinding of participants and blinding of outcome assessment. Incomplete outcome reporting and blinding of personnel showed mixed bias representations. Patient knowledge was assessed by four trials (160 participants) with moderate to substantial heterogeneity. There was evidence that educational programs improved patient knowledge, standardised mean difference 0.87 points (95% confidence interval 0.28 to 1.45, moderate quality evidence), which improved further when a trial with high bias was removed in a sensitivity analysis. Caregiver knowledge, reported in a single trial of 20 families, also showed an improvement, standardised mean difference 0.52 points (95% confidence interval 0.03 to 1.00, moderate quality evidence). The effect on patient knowledge was sustained at longer follow-up periods, whereas the effect on caregiver knowledge was not sustained. There were two primary outcomes related to the effectiveness of educational programs on the recognition of signs and symptoms of disease-related morbidity. No comparative data were reported for patients or caregivers (or both) recognising signs and symptoms leading to self-management. Data from two trials were analysed for the utilization of health services and showed no evidence of an effect, mean difference 0.33 (95% confidence interval -0.57 to 1.23, moderate quality evidence). With regard to the review's secondary outcomes, depression showed a statistically significant decline in intervention groups, standardised mean difference -0.66

points (95% confidence interval -1.18, to -0.14, moderate quality evidence). Adherence to treatment was not assessed in any of the identified trials. No effects of interventions were seen on coping, family relationships or health-related quality of life of patients. The quality of evidence was low for positive coping and moderate for child knowledge, healthcare utilization and depression. This suggests that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates.

### **AUTHORS' CONCLUSIONS:**

**This review identifies important positive effects of educational interventions on improving patient knowledge of sickle cell disease and depression.** Effects on patients' knowledge were maintained for longer than for caregivers. The effect on knowledge was significant but small and whether it offers any clinical benefit is uncertain. Significant factors limiting these effects could be trials being under powered as well as attrition rates. Effects were not statistically significant in assessments of secondary outcomes, possibly due to the paucity of the number of trials and patients and caregivers. Trials showed moderate to high heterogeneity which might impact the results. To better study effects on outcomes, further controlled trials are needed with rigorous attention given to improve recruitment and retention and to decrease bias. Predetermined protocols using similar measurements should be used across multiple sites.

Free access: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011175.pub2/full>

## HIV / AIDS

### Ante-retroviral therapy (ART)

[Pediatr Infect Dis J.](#) 2017 May;36(5):492-499. doi: 10.1097/INF.0000000000001481.

#### **Second- and Third-line Antiretroviral Therapy for Children and Adolescents: A Scoping Review.**

[Lazarus E](#)<sup>1</sup>, [Nicol S](#), [Frigati L](#), [Penazzato M](#), [Cotton MF](#), [Centeno-Tablante E](#), [Violari A](#), [Nicol L](#).

#### **Abstract**

#### **BACKGROUND:**

The World Health Organization identified a need for evidence to inform revision of second- and third-line antiretroviral therapy (ART) options in children failing ART. We performed an in-depth scoping review of all available literature on second-line and subsequent ART regimens in children younger than 18 years.

#### **METHODS:**

We comprehensively searched, without language or date limitations, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov.

#### **RESULTS:**

The search retrieved 1982 records. Eighteen studies provided efficacy data: 1 randomized controlled trial, 7 phase II trials, 5 prospective and 5 retrospective cohorts. **Five studies evaluated regimens in children failing first-line ART, 4 in children with multidrug resistance and 9 in children with variable treatment experience.** Only 10/18 studies reported week 48 or month 12 outcomes. **The overall proportion of children with virologic suppression defined by study at week 48 was 61.8%.** Although the randomized controlled trial had low risk of bias, outcomes were similar between groups because of highly active

optimized background regimens. All phase II and prospective studies were judged to have moderate to high risk of bias. **No study compared currently recommended lopinavir-based second-line regimens for nonnucleoside reverse transcriptase inhibitor failures to other non-nucleoside reverse transcriptase inhibitor regimens head-to-head.**

### CONCLUSIONS:

We found no evidence comparing current World Health Organization-recommended second- and third-line ART regimens with regimens including drugs of interest: raltegravir, darunavir, etravirine and atazanavir. Randomized controlled trials or prospective cohort studies with comparator arms, and bridging studies, ideally conducted in resource-limited settings, are required to guide future recommendations.

### Quality improvement intervention to increase adherence to ART prescription policy at HIV treatment clinics in Lusaka, Zambia: A cluster randomized trial.

McCarthy EA<sup>1</sup>, Subramaniam HL<sup>2</sup>, Prust ML<sup>2</sup>, Prescott MR<sup>2</sup>, Mpasela F<sup>3</sup>, Mwango A<sup>4</sup>, Namonje L<sup>5</sup>, Moyo C<sup>4</sup>, Chibuye B<sup>3</sup>, van den Broek JW<sup>6</sup>, Hehman L<sup>7</sup>, Moberley S<sup>8</sup>.

### INTRODUCTION:

In urban areas, crowded HIV treatment facilities with long patient wait times can deter patients from attending their clinical appointments and picking up their medications, ultimately disrupting patient care and compromising patient retention and adherence.

### METHODS:

Formative research at eight facilities in Lusaka revealed that **only 46% of stable HIV treatment patients were receiving a three-month refill supply of antiretroviral drugs, despite it being national policy for stable adult patients.** We designed a quality improvement intervention to improve the operationalization of this policy. **We conducted a cluster-randomized controlled trial in sixteen facilities in Lusaka with the primary objective of examining the intervention's impact on the proportion of stable patients receiving three-month refills.** The secondary objective was examining whether the quality improvement intervention reduced facility congestion measured through two proxy indicators: daily volume of clinic visits and average clinic wait times for services.

### RESULTS:

The mean change in the proportion of three-month refills among control facilities from baseline to endline was 10% (from 38% to 48%), compared to a 25% mean change (an increase from 44% to 69%) among intervention facilities. This represents a significant 15% mean difference (95% CI: 2%-29%;  $P = 0.03$ ) in the change in proportion of patients receiving three-month refills. On average, control facilities had 15 more visits per day in the endline than in the baseline, while intervention facilities had 20 fewer visits per day in endline than in baseline, a mean difference of 35 fewer visits per day ( $P = 0.1$ ). The change in the mean facility total wait time for intervention facilities dropped 19 minutes between baseline and endline when compared to control facilities (95% CI: -10.2-48.5;  $P = 0.2$ ).

### CONCLUSION:

A more patient-centred service delivery schedule of three-month prescription refills for stable patients is viable. We encourage the expansion of this sustainable intervention in Zambia's urban clinics.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5395211/>

*Quality improvement projects like this are important. What was actually done? The intervention was multifaceted, but a major part was the appointment of a quality improvement officer from within the existing staff to support the provision of three-month refills. The QI officer had a checklist to administer at each facility, they monitored drug and laboratory stock levels, ensured health care worker implementation of the three-month refill policy, record and troubleshoot challenges faced by the facility, and communicated with those at the district level for resolution. Intervention facilities also had job aids reminding pharmacists of the three-month refill policy.*

[PLoS One](#). 2016 Dec 9;11(12):e0165140. doi: 10.1371/journal.pone.0165140. eCollection 2016. [Malaria in HIV-Infected Children Receiving HIV Protease-Inhibitor- Compared with Non-Nucleoside Reverse Transcriptase Inhibitor-Based Antiretroviral Therapy, IMPAACT P1068s, Substudy to P1060.](#) [Hobbs CV](#)<sup>1,2,3</sup>, [Gabriel EE](#)<sup>4</sup>, [Kamthunzi P](#)<sup>5</sup>, [Tegha G](#)<sup>5</sup>, [Tauzie J](#)<sup>5</sup>, [Petzold E](#)<sup>6</sup>, [Barlow-Mosha L](#)<sup>7</sup>, [Chi BH](#)<sup>8</sup>, [Li Y](#)<sup>2</sup>, [Ilmet T](#)<sup>2,9</sup>, [Kirmse B](#)<sup>10</sup>, [Neal J](#)<sup>1</sup>, [Parikh S](#)<sup>11</sup>, [Deygoo N](#)<sup>2</sup>, [Jean Philippe P](#)<sup>12</sup>, [Mofenson L](#)<sup>13</sup>, [Prescott W](#)<sup>14</sup>, [Chen J](#)<sup>1,15</sup>, [Musoke P](#)<sup>7,16</sup>, [Palumbo P](#)<sup>17</sup>, [Duffy PE](#)<sup>1</sup>, [Borkowsky W](#)<sup>2</sup>; [P1068s Study Team](#).

### Abstract

#### BACKGROUND:

HIV and malaria geographically overlap. HIV protease inhibitors kill malaria parasites in vitro and in vivo, but further evaluation in clinical studies is needed.

#### METHODS:

Thirty-one children from Malawi aged 4-62 months were followed every 3 months and at intercurrent illness visits for ≤47 months (September 2009-December 2011). We compared malaria parasite carriage by blood smear microscopy (BS) and confirmed clinical malaria incidence (CCM, or positive BS with malaria symptoms) in children initiated on HIV antiretroviral therapy (ART) with zidovudine, lamivudine, and either nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, or lopinavir-ritonavir (LPV-rtv), a protease inhibitor.

#### RESULTS:

We found an association between increased time to recurrent positive BS, but not CCM, when anti-malarial treatment and LPV-rtv based ART were used concurrently and when accounting for a LPV-rtv and antimalarial treatment interaction (adjusted HR 0.39; 95% CI (0.17,0.89); p = 0.03).

#### CONCLUSIONS:

LPV-rtv in combination with malaria treatment was associated with lower risk of recurrent positive BS, but not CCM, in HIV-infected children. Larger, randomized studies are needed to confirm these findings which may permit ART optimization for malaria-endemic settings.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5147802/>

## Early infant diagnosis

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

[J Acquir Immune Defic Syndr](#). 2016 Aug 1;72 Suppl 2:S197-201. doi: 10.1097/QAI.0000000000001050.

**Point-of-Care Virologic Testing to Improve Outcomes of HIV-Infected Children in Zambia: A Clinical Trial Protocol.**

[Chibwesha CJ](#)<sup>1</sup>, [Ford CE](#), [Mollan KR](#), [Stringer JS](#).

**Abstract**

**INTRODUCTION:**

In the absence of early infant diagnosis (EID) and immediate antiretroviral therapy (ART), some 50% of untreated HIV-infected infants die before age 2. Conventional EID requires sophisticated instruments that are typically placed in centralized or reference laboratories. In low-resource settings, centralized systems often lead to result turnaround times of several months, long delays in diagnosis, and adverse outcomes for HIV-infected children. Our clinical trial tests the effectiveness of a new point-of-care (POC) diagnostic technology to identify HIV-infected infants and start providing them life-saving ART as soon as possible.

**METHODS AND DESIGN:**

The study uses a randomized, controlled design to test whether the Alere q platform for HIV DNA polymerase chain reaction (PCR) testing improves outcomes of HIV-infected children in Zambia. **We aim to enroll 2867 HIV-exposed infants aged 4-12 weeks and to follow those who are HIV infected for 12 months as they receive HIV care at 6 public health facilities in Lusaka.** The trial's primary endpoint is the proportion of HIV-infected infants in each study arm who start ART and remain alive, in care, and virally suppressed 12 months after their diagnostic blood draw.

**DISCUSSION:**

Our trial will provide evidence for the incremental benefit of implementing a POC EID strategy in low-resource settings where only off-site PCR services are currently available. The results will be useful in guiding future decisions regarding investments in POC virologic testing as part of overall pediatric AIDS mitigation strategies in sub-Saharan Africa.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5113248/>

## Management of HIV-related conditions

[Paediatr Int Child Health](#). 2017 May;37(2):121-128. doi: 10.1080/20469047.2016.1260891.

Epub 2017 Feb 1.

**Early use of corticosteroids in infants with a clinical diagnosis of Pneumocystis jiroveci pneumonia in Malawi: a double-blind, randomised clinical trial.**

[Newberry L](#)<sup>1,2</sup>, [O'Hare B](#)<sup>1,2,3</sup>, [Kennedy N](#)<sup>1,2,4</sup>, [Selman A](#)<sup>1,2</sup>, [Omar S](#)<sup>1,2</sup>, [Dawson P](#)<sup>1,2</sup>, [Stevenson K](#)<sup>1,2</sup>, [Nishihara Y](#)<sup>1,2</sup>, [Lissauer S](#)<sup>1,2</sup>, [Molyneux E](#)<sup>1,2</sup>.

**Abstract**

**BACKGROUND:**

Pneumocystis jiroveci pneumonia (PJP) is the most common opportunistic infection in infants with vertically acquired HIV infection and the most common cause of death in HIV-infected infants.

**OBJECTIVES:**

To determine whether early administration of adjuvant corticosteroids in addition to standard treatment reduces mortality in infants with vertically acquired HIV and clinically diagnosed PJP when co-infection with cytomegalovirus and other pathogens cannot be excluded.



**METHODS:**

A double-blind placebo-controlled trial of adjuvant prednisolone treatment in HIV-exposed infants aged 2-6 months admitted to Queen Elizabeth Central Hospital, Blantyre who were diagnosed clinically with PJP was performed. All recruited infants were HIV-exposed, and the HIV status of the infant was confirmed by DNA-PCR. HIV-exposed and infected infants as well as HIV-exposed but non-infected infants were included in the study. The protocol provided for the addition of prednisolone to the treatment at 48 h if there was clinical deterioration or an independent indication for corticosteroid therapy in any patient not receiving it. Oral trimethoprim-sulfamethoxazole (TMP/SMX) therapy and full supportive treatment were provided according to established guidelines. Primary outcomes for all patients included survival to hospital discharge and 6-month post-discharge survival.

**RESULTS:**

It was planned to enroll 200 patients but the trial was stopped early because of recruitment difficulties and a statistically significant result on interim analysis. **Seventy-eight infants were enrolled between April 2012 and August 2014; 36 infants (46%) were randomised to receive corticosteroids plus standard treatment with TMP/SMX, and 42 infants (54%) received the standard treatment plus placebo. In an intention-to treat-analysis, the risk ratio of in-hospital mortality in the steroid group compared with the standard treatment plus placebo group was 0.53 [95% CI 0.29-0.97,  $p = 0.038$ ]. The risk ratio of mortality at 6 months was 0.63 (95% CI 0.41-0.95,  $p = 0.029$ ).** Two children who received steroids developed bloody stools while in hospital.

**CONCLUSION:**

In infants with a clinical diagnosis of PJP, early use of steroids in addition to conventional TMP/SMX therapy significantly reduced mortality in hospital and 6 months after discharge.

[AIDS](#). 2016 Nov 28;30(18):2823-2829.

**Reduced bacterial skin infections in HIV-infected African children randomized to long-term cotrimoxazole prophylaxis.**

[Prendergast AJ<sup>1</sup>](#), [Bwakura-Dangarembizi M](#), [Mugenyi P](#), [Lutaakome J](#), [Kekitiinwa A](#), [Thomason MJ](#), [Gibb DM](#), [Walker AS](#); [ARROW Trial Team](#).

**OBJECTIVE:**

To evaluate whether cotrimoxazole prophylaxis prevents common skin conditions in HIV-infected children.

**DESIGN:**

Open-label randomized controlled trial of continuing versus stopping daily cotrimoxazole (post-hoc analysis).

**SETTING:**

Three sites in Uganda and one in Zimbabwe.

**PARTICIPANTS:**

A total of 758 children aged more than 3 years receiving antiretroviral therapy (ART) for more than 96 weeks in the ARROW trial were randomized to stop ( $n=382$ ) or continue ( $n=376$ ) cotrimoxazole after median (interquartile range) 2.1(1.8, 2.2) years on ART.

**INTERVENTION:**

Continuing versus stopping daily cotrimoxazole.

**MAIN OUTCOME MEASURES:**

Nurses screened for signs/symptoms at 6-week visits. This was a secondary analysis of ARROW trial data, with skin complaints categorized blind to randomization as bacterial, fungal, or viral infections; dermatitis; pruritic papular eruptions (PPEs); or others (blisters,



## Randomised trials in child health in developing countries 2016-17

desquamation, ulcers, and urticaria). Proportions ever reporting each skin complaint were compared across randomized groups using logistic regression.

### RESULTS:

At randomization, median (interquartile range) age was 7 (4, 11) years and CD4 was 33% (26, 39); 73% had WHO stage 3/4 disease. **Fewer children continuing cotrimoxazole reported bacterial skin infections over median 2 years follow-up (15 versus 33%, respectively;  $P<0.001$ ), with similar trends for PPE ( $P=0.06$ ) and other skin complaints ( $P=0.11$ ), but not for fungal ( $P=0.45$ ) or viral ( $P=0.23$ ) infections or dermatitis ( $P=1.0$ ).** Bacterial skin infections were also reported at significantly fewer clinic visits (1.2 versus 3.0%,  $P<0.001$ ). Independent of cotrimoxazole, bacterial skin infections were more common in children aged 6-8 years, with current CD4 cell count less than 500 cells/ $\mu$ l, WHO stage 3/4, less time on ART, and lower socio-economic status.

### CONCLUSION:

Long-term cotrimoxazole prophylaxis reduces common skin complaints, highlighting an additional benefit for long-term prophylaxis in sub-Saharan Africa.

### Comment

*WHO recommends: In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood irrespective of whether ART is provided (<http://www.who.int/hiv/pub/guidelines/arv2013/December2014-ARVsupplement-chap8.pdf>)*

[Paediatr Int Child Health](#). 2016 Aug;36(3):189-97. doi: 10.1179/2046905515Y.0000000038.

### The aetiology of diarrhoea, pneumonia and respiratory colonization of HIV-exposed infants randomized to breast- or formula-feeding.

[Zash RM](#)<sup>1,2</sup>, [Shapiro RL](#)<sup>1,2,3</sup>, [Leidner J](#)<sup>4</sup>, [Wester C](#)<sup>2</sup>, [McAdam AJ](#)<sup>5</sup>, [Hodinka RL](#)<sup>6</sup>, [Thior I](#)<sup>2</sup>, [Moffat C](#)<sup>2</sup>, [Makhema J](#)<sup>2</sup>, [McIntosh K](#)<sup>7</sup>, [Essex M](#)<sup>2,3</sup>, [Lockman S](#)<sup>2,3,8</sup>.

### BACKGROUND:

Diarrhoea and pneumonia are common causes of childhood death in sub-Saharan Africa but there are few studies describing specific pathogens.

### OBJECTIVES:

The study aimed to describe the pathogens associated with diarrhoea, pneumonia and oropharyngeal colonization in children born to HIV-infected women (HIV-exposed infants).

### METHODS:

**The Mashi Study randomized 1200 HIV-infected women and their infants to breastfeed for 6 months with ZDV prophylaxis or formula-feed with 4 weeks of ZDV.** Children were tested for HIV by PCR at 1, 4, 7, 9 and 12 months and by ELISA at 18 months. Pre-defined subsets of children were sampled during episodes of diarrhoea ( $n=300$ ) and pneumonia ( $n=85$ ). Stool was tested for bacterial pathogens, rotavirus and parasites. Children with pneumonia underwent bacterial blood culture, and testing of nasopharyngeal aspirates for viral pathogens by PCR. Oropharyngeal swabs were collected from a consecutive subset of 561 infants at the routine 3-month visit for bacterial culture.

### RESULTS:

The median age (range) at sampling was 181 days for diarrhoea (0-730) and 140 days for pneumonia (2-551). Pathogens were identified in 55 (18%) children with diarrhoea and 32 (38%) with pneumonia. **No differences in pathogens by child HIV status (HIV-infected vs HIV-uninfected) or feeding strategy were identified.** Campylobacter was the most common diarrhoeal pathogen (7%). Adenovirus (22%) and other viruses (19%) were the primary pathogens isolated during pneumonias. **More formula-fed infants had oropharyngeal**

**colonization by pathogenic Gram-negative bacteria (16.8% vs 6.2%,  $P = 0.003$ ), which was associated with a non-significant increased risk of pneumonia (OR 2.2, 95% CI 0.8-5.7).**

**CONCLUSION:**

A trend toward oropharyngeal bacterial colonization was observed in formula-fed infants. Although viruses were most commonly detected during pneumonia, respiratory colonization by Gram-negative bacteria may have contributed to pneumonia in formula-fed infants.

## Nutrition, growth and development of children with HIV

[Public Health Nutr.](#) 2017 Jun;20(8):1481-1490. doi: 10.1017/S1368980016003657. Epub 2017 Feb 8.

**[Exclusive breast-feeding promotion among HIV-infected women in South Africa: an Information-Motivation-Behavioural Skills model-based pilot intervention.](#)**

[Tuthill EL](#)<sup>1</sup>, [Butler LM](#)<sup>2</sup>, [Pellowski JA](#)<sup>3</sup>, [McGrath JM](#)<sup>4</sup>, [Cusson RM](#)<sup>4</sup>, [Gable RK](#)<sup>5</sup>, [Fisher JD](#)<sup>2</sup>.

**OBJECTIVE:**

Exclusive breast-feeding (EBF) provides optimal nutrition for infants and mothers. The practice of EBF while adhering to antiretroviral medication decreases the risk of mother-to-child transmission of HIV from approximately 25 % to less than 5 %. Thus the WHO recommends EBF for the first 6 months among HIV-infected women living in resource-limited settings; however, EBF rates remain low. In the present study our aim was to design and implement a pilot intervention promoting EBF among HIV-infected women.

**DESIGN:**

**The Information-Motivation-Behavioural Skills (IMB) model was applied in a brief motivational interviewing counselling session** that was tested in a small randomized controlled trial.

**SETTING:**

Pietermaritzburg, South Africa, at two comparable rural public health service clinics.

**SUBJECTS:**

Sixty-eight HIV-infected women in their third trimester were enrolled and completed baseline interviews between June and August 2014. Those randomized to the intervention arm received the IMB-based pilot intervention directly following baseline interviews. Follow-up interviews occurred at 6 weeks postpartum.

**RESULTS:**

While not significantly different between trial arms, high rates of intention and practice of EBF at 6-week follow-up were reported. Findings showed high levels of self-efficacy being significantly predictive of breast-feeding initiation and duration regardless of intervention arm.

**CONCLUSIONS:**

Future research must account for breast-feeding self-efficacy on sustaining breast-feeding behaviour and leverage strategies to enhance self-efficacy in supportive interventions. Supporting breast-feeding behaviour through programmes that include both individual-level and multi-systems components targeting the role of health-care providers, family and community may create environments that value and support EBF behaviour.

[Clin Med Insights Pediatr.](#) 2017 Jan 8;10:119-130. doi: 10.4137/CMPed.S40134. eCollection 2016.

**Early Benefits of a Starter Formula Enriched in Prebiotics and Probiotics on the Gut Microbiota of Healthy Infants Born to HIV+ Mothers: A Randomized Double-Blind Controlled Trial.**

Cooper P<sup>1</sup>, Bolton KD<sup>2</sup>, Velaphi S<sup>3</sup>, de Groot N<sup>4</sup>, Emady-Azar S<sup>5</sup>, Pecquet S<sup>4</sup>, Steenhout P<sup>6</sup>.

**Abstract**

The gut microbiota of infants is shaped by both the mode of delivery and the type of feeding. The gut of vaginally and cesarean-delivered infants is colonized at different rates and with different bacterial species, leading to differences in the gut microbial composition, which may persist up to 6 months. In a multicenter, randomized, controlled, double-blind trial conducted in South Africa, **we tested the effect of a formula supplemented with a prebiotic (a mixture of bovine milk-derived oligosaccharides [BMOS] generated from whey permeate and containing galactooligosaccharides and milk oligosaccharides such as 3'- and 6'-sialyllactose) and the probiotic *Bifidobacterium animalis* subsp. *lactis* (*B. lactis*) strain CNCM I-3446 on the bifidobacteria levels in the gut of infants born vaginally or via cesarean section in early life.** Additionally, the safety of the new formulation was evaluated. A total of 430 healthy, full-term infants born to HIV-positive mothers who had elected to feed their child beginning from birth ( $\leq 3$  days old) exclusively with formula were randomized into this multicenter trial of four parallel groups. A total of 421 infants who had any study formula intake were included in the full analysis set (FAS). The first two groups consisted of cesarean-delivered infants assigned to the Test formula ( $n = 92$ ) (a starter infant formula [IF] containing BMOS at a total oligosaccharide concentration of  $5.8 \pm 1.0$  g/100 g of powder formula [8 g/L in the reconstituted formula] + *B. lactis* [ $1 \times 10^7$  colony-forming units {cfu}/g]) or a Control IF ( $n = 101$ ); the second two groups consisted of vaginally delivered infants randomized to the same Test ( $n = 115$ ) or Control ( $n = 113$ ) formulas from the time of enrollment to 6 months. **The primary efficacy outcome was fecal bifidobacteria count at 10 days, and the primary safety outcome was daily weight gain (g/d) between 10 days and 4 months. At 10 days, fecal bifidobacteria counts were significantly higher in the Test formula than in the Control formula group among infants with cesarean birth (median [range] log: 9.41 [6.30-10.94] cfu/g versus 6.30 [6.30-10.51] cfu/g;  $P = 0.002$ ) but not among those with vaginal birth (median [range] log: 10.06 [5.93-10.77] cfu/g versus 9.85 [6.15-10.79] cfu/g;  $P = 0.126$ ).** The lower bound of the two-sided 95% confidence interval of the difference in the mean daily weight gain between the Test and Control formula groups was more than -3 g/d in both the vaginally and cesarean-delivered infants, indicating that growth in the Test formula-fed infants was not inferior to that of Control formula-fed infants. At 10 days and 4 weeks, the fecal pH of infants fed the Test formula was significantly lower than in those fed the Control formula, irrespective of mode of delivery: for vaginal delivery: 4.93 versus 5.59;  $P < 0.001$  (10 days) and 5.01 versus 5.71;  $P < 0.001$  (4 weeks); for cesarean delivery: 5.14 versus 5.65,  $P = 0.009$  (10 days) and 5.06 versus 5.75,  $P < 0.001$  (4 weeks). At 3 months, this acidification effect only persisted among cesarean-born infants. **IF supplemented with the prebiotic BMOS and probiotic *B. lactis* induced a strong bifidogenic effect in both delivering modes, but more explicitly correcting the low bifidobacteria level found in cesarean-born infants from birth.** The supplemented IF lowered the fecal pH and improved the fecal microbiota in both normal and cesarean-delivered infants. **The use of bifidobacteria as a probiotic even in infants who are immunologically at risk is safe and well tolerated.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5221488/>

J Nutr. 2017 Mar;147(3):453-461. doi: 10.3945/jn.116.242339. Epub 2017 Jan 25.

**Formula-Feeding of HIV-Exposed Uninfected African Children Is Associated with Faster Growth in Length during the First 6 Months of Life in the Kesho Bora Study.**  
[Bork KA](#)<sup>1</sup>, [Cames C](#)<sup>2</sup>, [Newell ML](#)<sup>3</sup>, [Read JS](#)<sup>4</sup>, [Ayassou K](#)<sup>5</sup>, [Musyoka F](#)<sup>6</sup>, [Mbatia G](#)<sup>7</sup>, [Cournil A](#)<sup>2</sup>; [Kesho Bora Study Group](#).

**Background:** Early feeding patterns may affect the growth of HIV-exposed children and thus their subsequent health and cognition.

**Objective:** We assessed the association of infant feeding (IF) mode with length-for-age z score (LAZ) and stunting from age 2 d to 18 mo in HIV-exposed African children within a controlled randomized trial, which evaluated triple antiretrovirals initiated during pregnancy and continued for 6 mo postpartum to prevent HIV transmission.

**Methods:** HIV-infected pregnant women with CD4<sup>+</sup> counts of 200-500 cells/mm<sup>3</sup> from Burkina Faso, Kenya, and South Africa were advised to exclusively breastfeed for up to 6 mo or to formula-feed from birth. Factors associated with LAZ were investigated in all uninfected children by using mixed-effects linear models; those associated with stunting (LAZ <-2) at 6 or 12 mo were assessed in multiple logistic regression after exclusion of children stunted at age 2 d. Independent variables were IF mode: formula feeding (FF), exclusive breastfeeding (EBF) <3 mo, or EBF ≥3 mo (reference); sex; trial arm; maternal characteristics; and site.

**Results:** Among 728 children, FF was associated with a greater increase in LAZ from 2 d to 6 mo (+0.07 z score/mo,  $P < 0.001$ ). Between 6 and 18 mo, FF and EBF <3 mo were both associated with greater mean LAZ than was EBF ≥3 mo (+0.52 z scores and +0.43 z scores, respectively,  $P < 0.001$ ). Among children not stunted at 2 d, FF was independently associated with a reduced risk of stunting at 6 mo (OR: 0.24; 95% CI: 0.07, 0.81;  $P = 0.021$ ), whereas EBF <3 mo was not (OR: 0.49; 95% CI: 0.22, 1.10;  $P = 0.09$ ).

**Conclusions:** In this observational study of HIV-exposed uninfected infants, growth in length in the first 6 mo of life was faster in formula-fed infants than in exclusively breastfed infants. The plausibility of residual confounding and reverse causality is discussed. This trial was registered at [www.controlled-trials.com](http://www.controlled-trials.com) as ISRCTN71468401.

[Public Health Nutr.](#) 2016 Jul;19(10):1904-12. doi: 10.1017/S1368980015003456. Epub 2015 Dec 7.

**Leaf concentrate compared with skimmed milk as nutritional supplementation for HIV-infected children: a randomized controlled trial in Burundi.**

[Collin SM](#)<sup>1</sup>, [Leclercq B](#)<sup>2</sup>, [Twungubumwe N](#)<sup>3</sup>, [Andréoletti L](#)<sup>4</sup>, [Richardier FC](#)<sup>2</sup>, [Bertin E](#)<sup>5</sup>.

**OBJECTIVE:**

The effectiveness of leaf concentrate powder (LCP) as a nutritional supplement was established in trials conducted among adolescent girls and pregnant women in India. Here we evaluate LCP, compared with skimmed milk powder (SMP), as a supplement for antiretroviral-naïve children living with HIV in a sub-Saharan African country.

**DESIGN:**

Randomized controlled, two-arm, 6-month trial comparing effects of isoproteic (5 g) LCP (10 g daily) and SMP (15 g daily) on HIV-1 viral load, CD4<sup>+</sup> cell count/percentage, weight/height-for-age, general blood parameters, diarrhoea, respiratory and HIV-related opportunistic infections.

**SETTING:**

Bujumbura and Kirundo, Burundi.

**SUBJECTS:**

Eighty-three HIV-positive, antiretroviral-naïve children aged 5-14 years: median (range) CD4<sup>+</sup> count, 716 (361-1690) cells/mm<sup>3</sup>; log<sub>10</sub> HIV-1 viral load, 4.39 (1.79-6.00).

### RESULTS:

LCP was equivalent to SMP in relation to HIV-specific blood parameters and did not demonstrate superiority over SMP in relation to Hb. Three children in each arm (LCP, 7.1 % (3/42); SMP, 7.3 % (3/41)) proceeded to antiretroviral therapy because their CD4+ counts fell below 350 cells/mm<sup>3</sup>. Children in the LCP group reported higher levels of appetite and overall health at 6 months. There were no differences in clinical events or any other outcome measures. LCP was less palatable than SMP to the children in this population, but there were few negative perceptions of appearance, texture and taste.

### CONCLUSIONS:

LCP appears to be equivalent to SMP as a nutritional supplement in this population, despite slightly lower palatability. In relation to viral load and CD4+ count, equivalence may indicate no effect in either group. Effectiveness relative to no supplementation remains to be determined.

Free access: [https://www.cambridge.org/core/services/aop-cambridge-core/content/view/14F754732A799025C25381EE938D92DA/S1368980015003456a.pdf/leaf\\_concentrate\\_compared\\_with\\_skimmed\\_milk\\_as\\_nutritional\\_supplementation\\_for\\_hivinfected\\_children\\_a\\_randomized\\_controlled\\_trial\\_in\\_burundi.pdf](https://www.cambridge.org/core/services/aop-cambridge-core/content/view/14F754732A799025C25381EE938D92DA/S1368980015003456a.pdf/leaf_concentrate_compared_with_skimmed_milk_as_nutritional_supplementation_for_hivinfected_children_a_randomized_controlled_trial_in_burundi.pdf)

[Trials](#). 2016 Nov 9;17(1):538.

### Improving early childhood care and development, HIV-testing, treatment and support, and nutrition in Mokhotlong, Lesotho: study protocol for a cluster randomized controlled trial.

[Tomlinson M](#)<sup>1</sup>, [Skeen S](#)<sup>2</sup>, [Marlow M](#)<sup>2</sup>, [Cluver L](#)<sup>3,4</sup>, [Cooper P](#)<sup>2,5</sup>, [Murray L](#)<sup>2,5</sup>, [Mofokeng S](#)<sup>2</sup>, [Morley N](#)<sup>6</sup>, [Makhetha M](#)<sup>6</sup>, [Gordon S](#)<sup>2</sup>, [Esterhuizen T](#)<sup>7</sup>, [Sherr L](#)<sup>8</sup>.

### BACKGROUND:

Since 1990, the lives of 48 million children under the age of 5 years have been saved because of increased investments in reducing child mortality. However, despite these unprecedented gains, 250 million children younger than 5 years in low- and middle-income countries (LMIC) cannot meet their developmental potential due to poverty, poor health and nutrition, and lack of necessary stimulation and care. Lesotho has high levels of poverty, HIV, and malnutrition, all of which affect child development outcomes. There is a unique opportunity to address these complex issues through the widespread network of informal preschools in rural villages in the country, which provide a setting for inclusive, integrated Early Childhood Care and Development (ECCD) and HIV and nutrition interventions.

### METHODS:

We are conducting a cluster randomised controlled trial in Mokhotlong district, Lesotho, to **evaluate a newly developed community-based intervention program to integrate HIV-testing and treatment services, ECCD, and nutrition education for caregivers with children aged 1-5 years living in rural villages**. Caregivers and their children are randomly assigned by village to intervention or control condition. We select, train, and supervise community health workers recruited to implement the intervention, which consists of nine group-based sessions with caregivers and children over 12 weeks (eight weekly sessions, and a ninth top-up session 1 month later), followed by a locally hosted community health outreach day event. Group-based sessions focus on using early dialogic book-sharing to promote cognitive development and caregiver-child interaction, health-related messages, including motivation for HIV-testing and treatment uptake for young children, and locally appropriate nutrition education. All children aged 1-5 years and their primary caregivers living in study villages are eligible for participation. Caregivers and their children will be interviewed and assessed at baseline, after completion of the intervention, and 12 months post intervention.



### DISCUSSION:

This study provides a unique opportunity to assess the potential of an integrated early childhood development intervention to prevent or mitigate developmental delays in children living in a context of extreme poverty and high HIV rates in rural Lesotho. This paper presents the intervention content and research protocol for the study.

### TRIAL REGISTRATION:

The Mphatlalatsane: Early Morning Star trial is registered on the International Standard Randomized Controlled Trial Number database, registration number ISRCTN16654287 ; the trial was registered on 3 July 2015.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5103333/>

## Prevention of parent to child transmission of HIV

[N Engl J Med](#). 2016 Nov 3;375(18):1726-1737.

### **Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention.**

[Fowler MG<sup>1</sup>](#), [Qin M<sup>1</sup>](#), [Fiscus SA<sup>1</sup>](#), [Currier JS<sup>1</sup>](#), [Flynn PM<sup>1</sup>](#), [Chipato T<sup>1</sup>](#), [McIntyre J<sup>1</sup>](#), [Gnanashanmugam D<sup>1</sup>](#), [Siberry GK<sup>1</sup>](#), [Coletti AS<sup>1</sup>](#), [Taha TE<sup>1</sup>](#), [Klingman KL<sup>1</sup>](#), [Martinson FE<sup>1</sup>](#), [Owor M<sup>1</sup>](#), [Violari A<sup>1</sup>](#), [Moodley D<sup>1</sup>](#), [Theron GB<sup>1</sup>](#), [Bhosale R<sup>1</sup>](#), [Bobat R<sup>1</sup>](#), [Chi BH<sup>1</sup>](#), [Strehlau R<sup>1</sup>](#), [Mlay P<sup>1</sup>](#), [Loftis AJ<sup>1</sup>](#), [Browning R<sup>1</sup>](#), [Fenton T<sup>1</sup>](#), [Purdue L<sup>1</sup>](#), [Basar M<sup>1</sup>](#), [Shapiro DE<sup>1</sup>](#), [Mofenson LM<sup>1</sup>](#); [IMPAACT 1077BF/1077FF PROMISE Study Team](#).

### BACKGROUND:

Randomized-trial data on the risks and benefits of antiretroviral therapy (ART) as compared with zidovudine and single-dose nevirapine to prevent transmission of the human immunodeficiency virus (HIV) in HIV-infected pregnant women with high CD4 counts are lacking.

### METHODS:

We randomly assigned **HIV-infected women at 14 or more weeks of gestation with CD4 counts of at least 350 cells per cubic millimeter to zidovudine and single-dose nevirapine plus a 1-to-2-week postpartum "tail" of tenofovir and emtricitabine (zidovudine alone); zidovudine, lamivudine, and lopinavir-ritonavir (zidovudine-based ART); or tenofovir, emtricitabine, and lopinavir-ritonavir (tenofovir-based ART).** The primary outcomes were HIV transmission at 1 week of age in the infant and maternal and infant safety.

### RESULTS:

The median CD4 count was 530 cells per cubic millimeter among 3490 primarily black African HIV-infected women enrolled at a median of 26 weeks of gestation (interquartile range, 21 to 30). **The rate of transmission was significantly lower with ART than with zidovudine alone (0.5% in the combined ART groups vs. 1.8%; difference, -1.3 percentage points; repeated confidence interval, -2.1 to -0.4).** However, the rate of maternal grade 2 to 4 adverse events was significantly higher with zidovudine-based ART than with zidovudine alone (21.1% vs. 17.3%,  $P=0.008$ ), and the rate of grade 2 to 4 abnormal blood chemical values was higher with tenofovir-based ART than with zidovudine alone (2.9% vs. 0.8%,  $P=0.03$ ). Adverse events did not differ significantly between the ART groups ( $P>0.99$ ). A birth weight of less than 2500 g was more frequent with zidovudine-based ART than with zidovudine alone (23.0% vs. 12.0%,  $P<0.001$ ) and was more frequent with tenofovir-based ART than with zidovudine alone (16.9% vs. 8.9%,  $P=0.004$ ); preterm delivery before 37 weeks was more frequent with zidovudine-based ART than with zidovudine alone (20.5% vs. 13.1%,  $P<0.001$ ). Tenofovir-based ART was

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associated with higher rates than zidovudine-based ART of very preterm delivery before 34 weeks (6.0% vs. 2.6%,  $P=0.04$ ) and early infant death (4.4% vs. 0.6%,  $P=0.001$ ), but there were no significant differences between tenofovir-based ART and zidovudine alone ( $P=0.10$  and  $P=0.43$ ). **The rate of HIV-free survival was highest among infants whose mothers received zidovudine-based ART.**

### CONCLUSIONS:

**Antenatal ART resulted in significantly lower rates of early HIV transmission than zidovudine alone but a higher risk of adverse maternal and neonatal outcomes.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5214343/>

### Comment

*This is an important trial showing that Option B+, commencing ART in pregnant women at diagnosis is associated with lower rates of HIV transmission. However the ideal regimen to use is uncertain. In this trial, the group assigned to tenofovir-based ART had more preterm deliveries (<34 weeks,  $p=0.04$ ), and more infant deaths than the group assigned to zidovudine-based ART (4.4% vs. 0.6%,  $P<0.001$ ). As Option B+ becomes the standard way of preventing vertical transmission of HIV, more research is also needed on longer term outcomes, including cardiac risks of long-term ART.*

[J Acquir Immune Defic Syndr](#). 2017 Jun 1;75 Suppl 2:S207-S215. doi: 10.1097/QAI.0000000000001360.

### **Impact of Facility-Based Mother Support Groups on Retention in Care and PMTCT Outcomes in Rural Zimbabwe: The EPAZ Cluster-Randomized Controlled Trial.**

[Foster G<sup>1</sup>](#), [Orne-Gliemann J](#), [Font H](#), [Kangwende A](#), [Magezi V](#), [Sengai T](#), [Rusakaniko S](#), [Shumba B](#), [Zambezi P](#), [Maphosa T](#).

### **Author information**

#### **BACKGROUND:**

Prevention of mother-to-child transmission elimination goals are hampered by low rates of retention in care. **The Eliminating Paediatric AIDS in Zimbabwe project assessed whether mother support groups (MSGs) improve rates of retention in care of HIV-exposed infants and their HIV-positive mothers, and maternal and infant outcomes.**

#### **METHODS:**

The study involved 27 rural clinics in eastern Zimbabwe. MSGs were established in 14 randomly selected clinics and met every 2 weeks coordinated by volunteer HIV-positive mothers. MSG coordinators provided health education and reminded mothers of MSG meetings by cell phone. **Infant retention in care was defined as "12 months postpartum point attendance" at health care visits of HIV-exposed infants at 12 months of age.** We also measured regularity of attendance and other program indicators of HIV-positive mothers and their HIV-exposed infants.

#### **RESULTS:**

Among 507 HIV-positive pregnant women assessed as eligible, 348 were enrolled and analyzed (69%) with mothers who had disclosed their HIV status being overrepresented. **In the intervention arm, 69% of infants were retained in care at 12 months versus 61% in the control arm, with no statistically significant difference.** Retention and other program outcomes were systematically higher in the intervention versus control arm, suggesting trends toward positive health outcomes with exposure to MSGs.

#### **DISCUSSION:**



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We were unable to show that facility-based MSGs improved retention in care at 12 months among HIV-exposed infants. Selective enrollment of mothers more likely to be retained-in-care may have contributed to lack of effect. Methods to increase the impact of MSGs on retention including targeting of high-risk mothers are discussed.

[Pan Afr Med J.](#) 2016 Dec 7;25:229. doi: 10.11604/pamj.2016.25.229.10014. eCollection 2016.  
[A descriptive study on demographic and behavioral characteristics of males and their responses to a male involvement intervention in Blantyre, Malawi.](#)  
[Nyondo-Mipando AL](#)<sup>1</sup>, [Chimwaza AF](#)<sup>2</sup>, [Muula AS](#)<sup>3</sup>.

### INTRODUCTION:

Male involvement (MI) remains a key factor in the enrollment and retention of pregnant women in the Prevention of Mother to child transmission (PMTCT) of Human Immunodeficiency Virus (HIV) services. The objective of this study was to describe the characteristics of men who accompanied their partners for PMTCT services and secondly, describe the reported reasons for the non-reporting by men for the services in Blantyre, Malawi.

### METHODS:

All men included in this analysis were partners of pregnant women enrolled in a MI in PMTCT randomized controlled trial (RCT), which took place in Blantyre, Malawi from 14 June 2013 to 24 February 2014. After randomization women were asked to invite their male partners for PMTCT services either through an invitation card or word of mouth invite. Descriptive statistics were tabulated using Stata.

### RESULTS:

Of the 462 women randomized, 109 (23.59%) women came back to the clinic with their male partner following the intervention. The majority, 307 (66.5%) women returned to the clinic without their partners. Although most men accepted the intervention, some failed to accompany their partners because of work obligations, a lack of interest in accompanying their partners for the service, and others promised to report at the next clinic visit.

### CONCLUSION:

The characteristics of men that reported were similar in the two groups, suggesting that demographic characteristics may not greatly influence their decision to be involved in PMTCT services. There is need to develop more flexible strategies to include men in PMTCT programmes.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5337293/>

[J Acquir Immune Defic Syndr.](#) 2016 Dec 15;73(5):572-580.

### [Maternal and Breastmilk Viral Load: Impacts of Adherence on Peripartum HIV Infections Averted-The Breastfeeding, Antiretrovirals, and Nutrition Study.](#)

[Davis NL](#)<sup>1</sup>, [Miller WC](#), [Hudgens MG](#), [Chasela CS](#), [Sichali D](#), [Kayira D](#), [Nelson JA](#), [Fiscus SA](#), [Tegha G](#), [Kamwendo DD](#), [Rigdon J](#), [Stringer JS](#), [Juliano JJ](#), [Ellington SR](#), [Kourtis AP](#), [Jamieson DJ](#), [van der Horst C](#); [BAN study team](#).

### BACKGROUND:

Antiretroviral (ARV) interventions are used to reduce HIV viral replication and prevent mother-to-child transmission. Viral suppression relies on adherence to ARVs.

### METHODS:

A 2-phase study was conducted using data from the Breastfeeding, Antiretrovirals, and Nutrition study. We included mothers randomized to 28 weeks of postpartum ARVs with  $\geq 1$  plasma or

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breastmilk specimen. All mothers who transmitted HIV to their infants from 2-28 weeks (n = 31) and 15% of mothers who did not (n = 232) were included. Adherence was measured by pill count [categorized as poor (0%-80%), partial (81%-98%), and near perfect (>98%)].

Associations between adherence and breastmilk RNA were assessed using mixed-effects models. Cox models were used to estimate associations between breastmilk RNA and HIV transmission. Using Monte Carlo simulation, we estimated the number of transmissions that would occur had everyone randomized to maternal ARVs been 90% and 100% adherent.

### RESULTS:

**Partial or near perfect ARV adherence significantly reduced the odds of having detectable ( $\geq 40$  copies/mL) breastmilk RNA, compared with poor adherence (Odds Ratio (OR) 0.23, 95% CI: 0.08 to 0.67; OR 0.36, 95% CI: 0.16 to 0.81, respectively).** Detectable breastmilk RNA was associated with increased breastmilk transmission compared with undetectable breastmilk RNA (hazard ratio 3.8, 95% CI: 1.2 to 12.1). All transmitting mothers had  $\geq 1$  plasma viral load specimen  $> 100$  copies per milliliter. An estimated similar number of transmissions would occur with 90% adherence compared with 100%.

### CONCLUSIONS:

Helping patients adhere to ARVs throughout breastfeeding is important for realizing the full potential of recommended ARV interventions to prevent mother-to-child HIV transmission. Maintaining plasma viral load  $< 100$  copies per milliliter may prevent breastmilk transmission.

[J Acquir Immune Defic Syndr](#). 2016 Aug 1;72 Suppl 2:S124-9. doi: 10.1097/QAI.0000000000001062.

**[Conditional Cash Transfers to Increase Retention in PMTCT Care, Antiretroviral Adherence, and Postpartum Virological Suppression: A Randomized Controlled Trial.](#)**  
[Yotebieng M](#)<sup>1</sup>, [Thirumurthy H](#), [Moracco KE](#), [Edmonds A](#), [Tabala M](#), [Kawende B](#), [Wenzi LK](#), [Okitolonda EW](#), [Behets F](#).

### BACKGROUND:

Novel strategies are needed to increase retention in prevention of mother-to-child HIV transmission (PMTCT) services. We have recently shown that small, incremental cash transfers conditional on attending clinic resulted in increased retention along the PMTCT cascade. However, whether women who receive incentives to attend clinic visits are as adherent to antiretrovirals (ARV) as those who do not was unknown.

### OBJECTIVE:

To determine whether HIV-infected women who received incentives to remain in care were as adherent to antiretroviral treatment and achieved the same level of viral suppression at 6 weeks postpartum as those who did not receive incentives but also remained in care.

### METHODS:

Newly diagnosed HIV-infected women at  $\leq 32$  weeks gestational age were recruited at antenatal care clinics in Kinshasa, Democratic Republic of Congo. Women were randomized in a 1:1 ratio to an intervention or control group. **The intervention group received compensation (\$5, plus \$1 increment at each subsequent visit) conditional on attending scheduled clinic visits and accepting offered PMTCT services, whereas the control group received usual care. The proportion of participants who remained in care, were fully adherent (took all their pills at each visit) or with undetectable viral load at 6 weeks postpartum were compared across group.**

### RESULTS:

Among 433 women randomized (216 in intervention group and 217 in control group), 332 (76.7%) remained in care at 6 weeks postpartum, including 174 (80.6%) in the intervention group and 158 (72.8%) in the control group, (P = 0.04). Data on pill count were available for

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297 participants (89.5%), including 156 (89.7%) and 141 (89.2%) in the intervention and control groups, respectively; 69.9% (109/156) and 68.1% (96/141) in the intervention and control groups had perfect adherence [risk difference, 0.02; 95% CI: -0.06 to 0.09]. Viral load results were available for 171 (98.3%) and 155 (98.7%) women in the intervention and control groups, respectively; 66.1% (113/171) in the intervention group and 69.7% (108/155) in the control group had an undetectable viral load (risk difference, -0.04; 95% CI: -0.14 to 0.07). Results were similar after adjusting for marital status, age, education, baseline CD4 count, viral load, gestational age, and initial ARV regimen.

### CONCLUSIONS:

**Although the provision of cash incentives to HIV-infected pregnant women led to higher retention in care at 6 weeks postpartum, among those retained in care, adherence to ARVs and virologic suppression did not differ by study group.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5113245/>

[J Acquir Immune Defic Syndr](#). 2017 Feb 1;74(2):150-157. doi: 10.1097/QAI.0000000000001219.

### Conditional Cash Transfers Improve Retention in PMTCT Services by Mitigating the Negative Effect of Not Having Money to Come to the Clinic.

[Yotebieng M](#)<sup>1</sup>, [Moracco KE](#), [Thirumurthy H](#), [Edmonds A](#), [Tabala M](#), [Kawende B](#), [Wenzi LK](#), [Okitolonda EW](#), [Behets F](#).

### Author information

#### OBJECTIVE:

To elucidate the mechanisms by which a cash incentive intervention increases retention in prevention of mother-to-child transmission services.

#### METHODS:

We used data from a randomized controlled trial in Kinshasa, Democratic Republic of Congo. Perceptual factors associated with loss to follow-up (LTFU) through 6 weeks postpartum were first identified. Then, binomial models were used to assess interactions between LTFU and identified factors, and the cash incentive intervention.

#### RESULTS:

Participants were less likely to be LTFU if they perceived HIV as a "very serious" health problem for their baby vs. not [risk difference (RD), -0.13; 95% confidence interval (CI): -0.30 to 0.04], if they believed it would be "very likely" to pass HIV to their baby if they did not take any HIV drug vs. not (RD, -0.15; 95% CI: -0.32 to 0.02), and if they anticipated that not having money would make it difficult for them to come to the clinic vs. not (RD, 0.12; 95% CI: -0.07 to 0.30). The effect of each of the 3 factors on LTFU was antagonistic to that of receiving the cash incentive intervention. The excess risk due to interaction between the cash incentive intervention and the anticipated difficulty of "not having money" to come to the clinic was exactly equal to the effect of removing this perceived barrier (excess risk due to interaction, -0.12; 95% CI: -0.35 to 0.10).

#### CONCLUSIONS:

Our analyses show that cash transfers improve retention in prevention of mother-to-child transmission services mainly by mitigating the negative effect of not having money to come to the clinic.

[J Acquir Immune Defic Syndr](#). 2016 Aug 1;72 Suppl 2:S137-44. doi: 10.1097/QAI.0000000000001060.

**Mother Infant Retention for Health (MIR4Health): Study Design, Adaptations, and Challenges With PMTCT Implementation Science Research.**

[Fayorsey RN<sup>1</sup>](#), [Chege D](#), [Wang C](#), [Reidy W](#), [Peters Z](#), [Syengo M](#), [Barasa C](#), [Owino SO](#), [Sirengo M](#), [Hawken MP](#), [Abrams EJ](#).

**Abstract**

**BACKGROUND:**

Effective retention of HIV-infected mothers and their infants is fraught with multiple challenges, resulting in loss across the continuum of prevention of mother-to-child HIV transmission (PMTCT) care and missed opportunities to offer life-saving HIV prevention and treatment.

**METHODS:**

The Mother Infant Retention for Health study is an individual-randomized study evaluating the effectiveness of active patient follow-up compared with standard of care on the combined outcome of attrition of HIV-infected women and their infants at 6 months postpartum. Lay counselors administered the active patient follow-up package of interventions, including individualized health education, use of flip charts during clinic visits, and at home, phone and short message service appointment reminders, active phone and physical tracking of patients immediately after missed clinic visits, and individualized retention and adherence support.

**RESULTS:**

Use of study visits to indicate participant progression along the PMTCT cascade highlights the nature of loss among women and infants in PMTCT care because of issues such as pregnancy complications, infant deaths, and transfer out. Delay in implementation of Option B+, unanticipated slow enrollment, a health-care worker strike, rapid HIV test kit shortages, and changes in national PMTCT guidelines necessitated several modifications to the protocol design and implementation to ensure successful completion of the study.

**CONCLUSIONS:**

Flexibility when operationalizing an implementation science study is critical in the context of the shifting landscape in a noncontrolled "real-world" setting.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5113246/>

[J Acquir Immune Defic Syndr](#). 2016 Aug 1;72 Suppl 2:S130-6. doi: 10.1097/QAI.0000000000001059.

**A Protocol for a Cluster Randomized Trial on the Effect of a "feeding buddy" Program on adherence to the Prevention of Mother-To-Child-Transmission Guidelines in a Rural Area of KwaZulu-Natal, South Africa.**

[Reimers P<sup>1</sup>](#), [Israel-Ballard K](#), [Spies L](#), [Tanser F](#), [Thior I](#), [Scott Gordon W](#), [Coutsoudis A](#).

**BACKGROUND:**

The uptake of prevention of mother-to-child-transmission (PMTCT) services has improved in South Africa but challenges remain, including adherence to the World Health Organization's (WHO) PMTCT recommendations of exclusive breastfeeding (EBF), taking antiretroviral medication (ARV); testing for early infant diagnosis; and reducing stigma. **Women who practice EBF for the first 6 months are less likely to transmit HIV to their infants, yet only 7% of women EBF for 6 months in South Africa. Adherence to these recommendations remains challenging because of difficulties relating to disclosure and stigma.** To address this challenge, the feeding buddy concept was developed based on studies where ARV buddies have

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proved effective in providing support for women living with HIV. Buddies have demonstrated a positive effect on providing emotional and social support to adhere to PMTCT guidelines.

### METHODS:

A cluster randomized controlled trial was conducted in 16 selected randomly assigned clinics in uMhlathuze and uMlalazi districts of KwaZulu Natal, South Africa. HIV-positive pregnant women (n = 625) who intended to breastfeed were enrolled at 8 control clinics and 8 intervention clinics. The clinics were stratified on the basis of urban/rural/periurban locale and then randomly allocated to either intervention or control. **In the intervention clinics, the mother chose a feeding buddy to be enrolled alongside her.** Quantitative interviews with mothers and their chosen buddies took place at enrollment during pregnancy and at routine postdelivery visits at day 3 and weeks 6, 14 and 22. Women in the control clinics were followed using the same evaluation schedule. **The trial evaluated the effect of a voluntary PMTCT feeding buddy program on HIV-infected women's adherence to PMTCT recommendations and stigma reduction. The proportion of women exclusively feeding at 5.5 months postpartum was the primary end-point of the trial.** In-depth interviews were conducted among a convenience sample of PMTCT counselors, community caregivers, mothers, and buddies from intervention clinics and control clinics to document their overall experiences.

### DISCUSSION:

The information collected in this study could be used to guide recommendations on how to build upon the current South Africa. PMTCT "buddy" strategy and to improve safe infant feeding. The information would be applicable to many other similar resource poor settings with poor social support structures.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5113241/>

## Maternal HIV prevention strategies

[N Engl J Med.](#) 2016 Dec 1;375(22):2121-2132. Epub 2016 Feb 22.

### [Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women.](#)

[Baeten JM](#), [Palanee-Phillips T](#), [Brown ER](#), [Schwartz K](#), [Soto-Torres LE](#), [Govender V](#), [Mgodi NM](#), [Matovu Kiweewa F](#), [Nair G](#), [Mhlanga F](#), [Siva S](#), [Bekker LG](#), [Jeenarain N](#), [Gaffoor Z](#), [Martinson F](#), [Makanani B](#), [Pather A](#), [Naidoo L](#), [Husnik M](#), [Richardson BA](#), [Parikh UM](#), [Mellors JW](#), [Marzinke MA](#), [Hendrix CW](#), [van der Straten A](#), [Ramjee G](#), [Chirenje ZM](#), [Nakabiito C](#), [Taha TE](#), [Jones J](#), [Mayo A](#), [Scheckter R](#), [Berthiaume J](#), [Livant E](#), [Jacobson C](#), [Ndase P](#), [White R](#), [Patterson K](#), [Germuga D](#), [Galaska B](#), [Bunge K](#), [Singh D](#), [Szydlo DW](#), [Montgomery ET](#), [Mensch BS](#), [Torjesen K](#), [Grossman CI](#), [Chakhtoura N](#), [Nel A](#), [Rosenberg Z](#), [McGowan I](#), [Hillier S](#); [MTN-020-ASPIRE Study Team](#).

### Abstract

#### BACKGROUND:

Antiretroviral medications that are used as prophylaxis can prevent acquisition of human immunodeficiency virus type 1 (HIV-1) infection. However, in clinical trials among African women, the incidence of HIV-1 infection was not reduced, probably because of low adherence. Longer-acting methods of drug delivery, such as vaginal rings, may simplify use of antiretroviral medications and provide HIV-1 protection.

#### METHODS:

We conducted a phase 3, **randomized, double-blind, placebo-controlled trial of a monthly vaginal ring containing dapivirine, a non-nucleoside HIV-1 reverse-transcriptase inhibitor,**



involving women between the ages of 18 and 45 years in Malawi, South Africa, Uganda, and Zimbabwe.

### RESULTS:

Among the 2629 women who were enrolled, 168 HIV-1 infections occurred: 71 in the dapivirine group and 97 in the placebo group (incidence, 3.3 and 4.5 per 100 person-years, respectively).

**The incidence of HIV-1 infection in the dapivirine group was lower by 27% (95% confidence interval [CI], 1 to 46; P=0.046) than that in the placebo group.** In an analysis that excluded data from two sites that had reduced rates of retention and adherence, the incidence of HIV-1 infection in the dapivirine group was lower by 37% (95% CI, 12 to 56; P=0.007) than that in the placebo group. In a post hoc analysis, higher rates of HIV-1 protection were observed among women over the age of 21 years (56%; 95% CI, 31 to 71; P<0.001) but not among those 21 years of age or younger (-27%; 95% CI, -133 to 31; P=0.45), a difference that was correlated with reduced adherence. The rates of adverse medical events and antiretroviral resistance among women who acquired HIV-1 infection were similar in the two groups.

### CONCLUSIONS:

A monthly vaginal ring containing dapivirine reduced the risk of HIV-1 infection among African women, with increased efficacy in subgroups with evidence of increased adherence. (Funded by the National Institutes of Health; ClinicalTrials.gov number, [NCT01617096](https://www.clinicaltrials.gov/ct2/show/study?term=NCT01617096) ).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4993693/>

## HIV vaccine

(see Vaccine – HIV vaccine)

## Helminth and other gastrointestinal disorders

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

[Infect Dis Poverty](#). 2017 Feb 9;6(1):30. doi: 10.1186/s40249-017-0244-z.

**Impact of single annual treatment and four-monthly treatment for hookworm and *Ascaris lumbricoides*, and factors associated with residual infection among Kenyan school children.**

[Kepha S](#)<sup>1</sup>, [Mwandawiro CS](#)<sup>2</sup>, [Anderson RM](#)<sup>3</sup>, [Pullan RL](#)<sup>4</sup>, [Nuwaha F](#)<sup>5</sup>, [Cano J](#)<sup>4</sup>, [Njenga SM](#)<sup>2</sup>, [Odiere MR](#)<sup>6</sup>, [Allen E](#)<sup>4</sup>, [Brooker SJ](#)<sup>4,7</sup>, [Nikolay B](#)<sup>4</sup>.

### BACKGROUND:

School-based deworming is widely implemented in various countries to reduce the burden of soil-transmitted helminths (STHs), however, the frequency of drug administration varies in different settings. In this study, we compared **the impact of a single annual treatment and 4-monthly treatment over a follow-up among Kenyan school children**, and investigated the factors associated with residual infection.

### METHODS:

We performed a secondary analysis of data from a randomized trial investigating whether deworming for STHs alters risk of acquiring malaria. **Children received either a single treatment or 4-monthly albendazole treatments were followed longitudinally from February 2014 to October 2014.** The relative impact of treatment and factors associated with residual infections were investigated using mixed-effects regression models. Predisposition to infection was assessed based on Spearman's rank and Kendall's Tau correlation coefficients.

### RESULTS:

In the 4-monthly treatment group, the proportion of children infected with hookworm decreased from 59.9 to 5.7%, while *Ascaris lumbricoides* infections dropped from 55.7 to 6.2%. In the single treatment group, hookworm infections decreased over the same time period from 58.7 to 18.3% (12.6% absolute difference in reduction, 95% CI: 8.9-16.3%), and *A. lumbricoides* from 56.7 to 23.3% (17.1% absolute difference in reduction, 95% CI: 13.1-21.1%). There was strong evidence for predisposition to both STH types. Residual hookworm infection among children on 4-monthly treatment were associated with male sex and baseline nutritional status, whereas *A. lumbricoides* infection was associated with individual and school-level infection at baseline, latrine cleanliness at schools.

### CONCLUSIONS:

This study found that 4-monthly treatment was more effective than single annual treatment. Repeated treatments led to dramatic reductions in the intensities of STHs, but did not completely clear infections among school children in Kenya, a presumed reflection of reinfection in a setting where there is ongoing transmission.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5299645/>

[Am J Trop Med Hyg.](#) 2016 Jul 6;95(1):83-7. doi: 10.4269/ajtmh.15-0816. Epub 2016 May 2.  
**Adverse Events from a Randomized, Multi-Arm, Placebo-Controlled Trial of Mebendazole in Children 12-24 Months of Age.**

[Joseph SA](#)<sup>1</sup>, [Montresor A](#)<sup>2</sup>, [Casapía M](#)<sup>3</sup>, [Pezo L](#)<sup>3</sup>, [Gyorkos TW](#)<sup>4</sup>.

### Abstract

Large-scale deworming interventions, using anthelmintic drugs, are recommended in areas where the prevalence of soil-transmitted helminth infection is high. Anthelmintic safety has been established primarily in school-age children. Our objective was to provide evidence on adverse events from anthelmintic use in early childhood. **A randomized multi-arm, placebo-controlled trial of mebendazole, administered at different times and frequencies, was conducted in children 12 months of age living in Iquitos, Peru.** Children were followed up to 24 months of age. The association between mebendazole administration and the occurrence of a serious or minor adverse event was determined using logistic regression. There was a total of 1,686 administrations of mebendazole and 1,676 administrations of placebo to 1,760 children. Eighteen serious adverse events (i.e., 11 deaths and seven hospitalizations) and 31 minor adverse events were reported. **There was no association between mebendazole and the occurrence of a serious adverse event (odds ratio [OR] = 1.21; 95% confidence interval [CI] = 0.47, 3.09) or a minor adverse event (OR = 0.84; 95% CI = 0.41, 1.72).** Results from our trial support evidence of safety in administering mebendazole during early childhood. These results support World Health Organization deworming policy and the scaling up of interventions to reach children as of 12 months of age in endemic areas.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944715/>

## Hepatitis

[J Infect Dis.](#) 2016 Dec 1;214(11):1695-1699. Epub 2016 Sep 22.



**Hepatitis B Virus (HBV) Load Response to 2 Antiviral Regimens, Tenofovir/Lamivudine and Lamivudine, in HIV/ HBV-Coinfected Pregnant Women in Guangxi, China: The Tenofovir in Pregnancy (TiP) Study.**

[Wang L](#)<sup>1,2,3</sup>, [Wiener J](#)<sup>4</sup>, [Bulterys M](#)<sup>1,5</sup>, [Wei X](#)<sup>1</sup>, [Chen L](#)<sup>6</sup>, [Liu W](#)<sup>7</sup>, [Liang S](#)<sup>7</sup>, [Shepard C](#)<sup>1,5</sup>, [Wang L](#)<sup>8</sup>, [Wang A](#)<sup>8</sup>, [Zhang F](#)<sup>2,3,9</sup>, [Kourtis AP](#)<sup>4</sup>.

**Abstract**

**BACKGROUND:**

There is limited information on antiviral therapy for hepatitis B virus (HBV) infection among pregnant women coinfecting with human immunodeficiency virus (HIV) and HBV.

**METHODS:**

A phase 2 randomized, controlled trial of a regimen containing tenofovir (TDF)/lamivudine (3TC) and a regimen containing 3TC in HIV/HBV-coinfecting pregnant women in China. The HBV virological response was compared in study arms.

**RESULTS:**

The median decline in the HBV DNA level was 2.60 log<sub>10</sub> copies/mL in the TDF/3TC arm and 2.24 log<sub>10</sub> copies/mL in the 3TC arm (P = .41). All women achieved HBV DNA levels of <6 log<sub>10</sub> copies/mL at delivery.

**CONCLUSIONS:**

Initiation of either regimen led to achievement of HBV DNA levels below the threshold associated with perinatal HBV transmission.

## Injury prevention

## Integrated management of Childhood Illness (IMCI)

## Iodine deficiency

[Am J Clin Nutr.](#) 2016 Sep;104(3):620-8. doi: 10.3945/ajcn.116.134049. Epub 2016 Jul 27.

**A dose-response crossover iodine balance study to determine iodine requirements in early infancy.**

[Dold S](#)<sup>1</sup>, [Zimmermann MB](#)<sup>2</sup>, [Baumgartner J](#)<sup>3</sup>, [Davaz T](#)<sup>4</sup>, [Galetti V](#)<sup>4</sup>, [Braegger C](#)<sup>5</sup>, [Andersson M](#)<sup>2</sup>.

**Abstract**

**BACKGROUND:**

Optimal iodine intake during infancy is critical for brain development, but no estimated average requirement (EAR) is available for this age group.

**OBJECTIVE:**

We measured daily iodine intake, excretion, and retention over a range of iodine intakes in early infancy to determine the minimum daily intake required to achieve iodine balance.

**DESIGN:**

In a dose-response crossover study, **we randomly assigned healthy infants (n = 11; mean ± SD age 13 ± 3 wk) to sequentially consume over 33 d 3 infant formula milks (IFMs) containing 10.5, 19.3, and 38.5 µg I/100 kcal, respectively.** Each IFM was consumed for 11 d, consisting of a 6-d run-in period followed by a 4-d balance period and 1 run-out day.

**RESULTS:**

Iodine intake (mean ± SD: 54.6 ± 8.1, 142.3 ± 23.1, and 268.4 ± 32.6 µg/d), excretion (55.9 ± 8.6, 121.9 ± 21.7, and 228.7 ± 39.3 µg/d), and retention (-1.6 ± 8.3, 20.6 ± 21.6, and 39.8 ± 34.3 µg/d) differed among the low, middle, and high iodine IFM groups (P < 0.001 for all). There

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was a linear relation between daily iodine intake and both daily iodine excretion and daily iodine retention. Zero balance (iodine intake = iodine excretion, iodine retention = 0 µg/d) was achieved at a daily iodine intake of 70 µg (95% CI: 60, 80 µg).

### CONCLUSION:

**Our data indicate the iodine requirement in 2- to 5-mo-old infants is 70 µg/d.** Adding an allowance for accumulation of thyroidal iodine stores would produce an EAR of 72 µg and a recommended dietary allowance of 80 µg.

## Kidney disease

[Kidney Int.](#) 2017 Jul;92(1):248-257. doi: 10.1016/j.kint.2017.01.019. Epub 2017 Mar 18.

**[Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome.](#)**

[Sinha A](#)<sup>1</sup>, [Gupta A](#)<sup>1</sup>, [Kalaivani M](#)<sup>2</sup>, [Hari P](#)<sup>1</sup>, [Dinda AK](#)<sup>3</sup>, [Bagga A](#)<sup>4</sup>.

### Abstract

Studies of nephrotic syndrome show that substitution of calcineurin inhibitors by mycophenolate mofetil (MMF) enables sustained remission and corticosteroid sparing and avoids therapy associated adverse effects. However, controlled studies in patients with steroid resistance are lacking. **Here we examined the effect of switching from therapy with tacrolimus to MMF on disease course in an open-label, one-to-one randomized, controlled trial on children (one to 18 years old), recently diagnosed with steroid-resistant nephrotic syndrome, at a referral center in India. Following six months of therapy with tacrolimus, patients with complete or partial remission were randomly assigned such that 29 received MMF while 31 received tacrolimus along with tapering prednisolone on alternate days for 12 months. On intention-to-treat analyses, the proportion of patients with a favorable outcome (sustained remission, infrequent relapses) at one year was significantly lower (44.8%) in the MMF group than in the tacrolimus group (90.3%).** The incidence of relapses was significantly higher for patients treated with MMF than tacrolimus (mean difference: 1.05 relapses per person-year). While there was no difference in the proportion of patients with sustained remission, the risk of recurrence of steroid resistance was significantly higher for patients receiving MMF compared to tacrolimus (mean difference: 20.7%). Compared to tacrolimus, patients receiving MMF had a significantly (71%) lower likelihood of a favorable outcome and significantly increased risk of treatment failure (frequent relapses, steroid resistance). Thus, **replacing tacrolimus with MMF after six months of tacrolimus therapy for steroid-resistant nephrotic syndrome in children is associated with significant risk of frequent relapses or recurrence of resistance.** These findings have implications for guiding the duration of therapy with tacrolimus for steroid-resistant nephrotic syndrome.

## Leishmaniasis

[PLoS Negl Trop Dis.](#) 2016 Sep 14;10(9):e0004880. doi: 10.1371/journal.pntd.0004880. eCollection 2016 Sep.

**[Efficacy and Safety of AmBisome in Combination with Sodium Stibogluconate or Miltefosine and Miltefosine Monotherapy for African Visceral Leishmaniasis: Phase II Randomized Trial.](#)**

## Randomised trials in child health in developing countries 2016-17

[Wasunna M](#)<sup>1,2</sup>, [Njenga S](#)<sup>2</sup>, [Balasegaram M](#)<sup>3</sup>, [Alexander N](#)<sup>4</sup>, [Omollo R](#)<sup>1</sup>, [Edwards T](#)<sup>4</sup>, [Dorlo TP](#)<sup>5</sup>, [Musa B](#)<sup>6</sup>, [Ali MH](#)<sup>6</sup>, [Elamin MY](#)<sup>6</sup>, [Kirigi G](#)<sup>2</sup>, [Juma R](#)<sup>2</sup>, [Kip AE](#)<sup>5,7</sup>, [Schoone GJ](#)<sup>8</sup>, [Hailu A](#)<sup>9</sup>, [Olobo J](#)<sup>10</sup>, [Ellis S](#)<sup>3</sup>, [Kimutai R](#)<sup>1,2</sup>, [Wells S](#)<sup>3</sup>, [Khalil EA](#)<sup>6</sup>, [Strub Wourgaft N](#)<sup>3</sup>, [Alves F](#)<sup>3</sup>, [Musa A](#)<sup>6</sup>.

### BACKGROUND:

SSG&PM over 17 days is recommended as first line treatment for visceral leishmaniasis in eastern Africa, but is painful and requires hospitalization. Combination regimens including AmBisome and miltefosine are safe and effective in India, but there are no published data from trials of combination therapies including these drugs from Africa.

### METHODS:

A phase II open-label, non-comparative randomized trial was conducted in Sudan and Kenya to evaluate the efficacy and safety of three treatment regimens: **10 mg/kg single dose AmBisome plus 10 days of SSG (20 mg/kg/day), 10 mg/kg single dose AmBisome plus 10 days of miltefosine (2.5mg/kg/day) and miltefosine alone (2.5 mg/kg/day for 28 days)**. The primary endpoint was initial parasitological cure at Day 28, and secondary endpoints included definitive cure at Day 210, and pharmacokinetic (miltefosine) and pharmacodynamic assessments.

### RESULTS:

**In sequential analyses with 49-51 patients per arm, initial cure was 85% (95% CI: 73-92) in all arms. At D210, definitive cure was 87% (95% CI: 77-97) for AmBisome + SSG, 77% (95% CI 64-90) for AmBisome + miltefosine and 72% (95% CI 60-85) for miltefosine alone, with lower efficacy in younger patients, who weigh less.** Miltefosine pharmacokinetic data indicated under-exposure in children compared to adults.

### CONCLUSION:

No major safety concerns were identified, but **point estimates of definitive cure were less than 90% for each regimen so none will be evaluated in Phase III trials in their current form.** Allometric dosing of miltefosine in children needs to be evaluated.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023160/>

[Am J Trop Med Hyg](#). 2017 Jan 11;96(1):182-189. doi: 10.4269/ajtmh.16-0345. Epub 2016 Nov 22.

### **Effectiveness of Short-Course Meglumine Antimoniate (Glucantime®) for Treatment of Visceral Leishmaniasis: A 13-Year, Multistage, Non-Inferiority Study in Iran.**

[Alborzi A](#)<sup>1</sup>, [Pouladfar G](#)<sup>2</sup>, [Attar A](#)<sup>3,4,5</sup>, [Falahi F](#)<sup>6</sup>, [Jafarpour Z](#)<sup>1</sup>, [Karimi A](#)<sup>7</sup>, [Kadivar MR](#)<sup>1</sup>.

#### Abstract

The World Health Organization's (WHO) recommendation is 28-day course of meglumine antimoniate (Glucantime®, Sanofi Aventis, France) for the treatment of visceral leishmaniasis (VL). The aim of this study was to evaluate the effectiveness of a shorter duration of treatment in regions with low level of resistance to Glucantime. **During 13 years, this study was conducted in three phases on 392 patients.** In the pilot first phase, we performed splenic punctures in seven patients to assess the correlation between the changes in the parasite load during treatment with Glucantime and defervescence. With defervescence, parasite density was dramatically dropped ( $P = 0.014$ ), propounding defervescence as a marker of parasitological response. **On the basis of the results, we conducted a randomized trial on 75 patients, comparing the efficacy of continuation of Glucantime therapy for 1, 2, or 3 weeks after defervescence. The treatment course of 1 week after defervescence (mean = 11.7 days) was non-inferior to that of 3 weeks (final cure rate, 96% versus 100%;  $P = 0.023$ ).** The third phase was a retrospective cohort study of 302 patients treated either with the WHO's regimen or for 7 days after defervescence (intervention group). Relapse was detected in 8.3% patients of the intervention group and in 5% patients following the WHO's regimen ( $P = 0.006$  for non-

inferiority). The final duration of treatment in intervention group was significantly shorter than standard course ( $13.3 \pm 2.6$  versus 28 days;  $P < 0.001$ ). **In summary, treatment of VL with Glucantime for 1 week after defervescence was non-inferior to and appears to be an acceptable alternative to the standard 28-day course for patients in Iran who show a response to antimonial therapy.**

[Dermatol Ther.](#) 2016 Sep;29(5):358-363. doi: 10.1111/dth.12357. Epub 2016 Apr 12.  
[Topical liposomal azithromycin in the treatment of acute cutaneous leishmaniasis.](#)  
[Rajabi O](#)<sup>1,2</sup>, [Layegh P](#)<sup>3</sup>, [Hashemzadeh S](#)<sup>4</sup>, [Khoddami M](#)<sup>5</sup>.

### Abstract

Cutaneous leishmaniasis (CL) treatment is based on pentavalent antimony (sbv) drugs which are accompanied by many side effects and are facing ever-increasing resistance. Topical treatment of CL is an attractive alternative avoiding toxicities of parenteral therapy while being administered through a simple painless route. The liposomal formulations of different drugs have recently been increasingly used in the treatment of several types of leishmaniasis. **The efficacy of a topical liposomal azithromycin formulation was compared with intralesional meglumine antimoniate (glucantime) in the treatment of CL.** Sixty-six patients with 97 lesions who met our inclusion criteria were randomly divided into two groups. One group was administered with the topical liposomal form of azithromycin twice daily. The other group was treated by weekly intralesional injections of glucantime with a volume of 0.5-2 cm<sup>3</sup> into each lesion till complete blanching of the lesion occurred. Clinical evaluations were performed weekly during the treatment course (8 weeks) by a single dermatologist for both groups. Per-protocol analysis showed no statistically significant difference between the two groups ( $p = 0.84$ , 95% confidence interval (CI) = 0.764 (0.714-0.821). Serious drug side effects were not observed in either group. **Topical liposomal azithromycin has the same efficacy as intralesional glucantime in the treatment of CL.**

## Leprosy

## Malaria

(See also Maternal health, Anaemia)

[Malar J.](#) 2016 Jul 8;15:349. doi: 10.1186/s12936-016-1388-1.  
[Geo-spatial factors associated with infection risk among young children in rural Ghana: a secondary spatial analysis.](#)  
[Aimone AM](#)<sup>1</sup>, [Brown PE](#)<sup>2</sup>, [Zlotkin SH](#)<sup>3</sup>, [Cole DC](#)<sup>1</sup>, [Owusu-Agyei S](#)<sup>4</sup>.

### Abstract

#### BACKGROUND:

Determining the spatial patterns of infection among young children living in a malaria-endemic area may provide a means of locating high-risk populations who could benefit from additional resources for treatment and improved access to healthcare. The objective of this secondary analysis of baseline data from a cluster-randomized trial among 1943 young Ghanaian children (6-35 months of age) was to determine the geo-spatial factors associated with malaria and non-malaria infection status.

### METHODS:

Spatial analyses were conducted using a generalized linear geostatistical model with a Matern spatial correlation function and four definitions of infection status using different combinations of inflammation (C-reactive protein, CRP > 5 mg/L) and malaria parasitaemia (with or without fever). Potentially informative variables were included in a final model through a series of modelling steps, including: individual-level variables (Model 1); household-level variables (Model 2); and, satellite-derived spatial variables (Model 3). A final (Model 4) and maximal model (Model 5) included a set of selected covariates from Models 1 to 3.

### RESULTS:

**The final models indicated that children with inflammation (CRP > 5 mg/L) and/or any evidence of malaria parasitaemia at baseline were more likely to be under 2 years of age, stunted, wasted, live further from a health facility, live at a lower elevation, have less educated mothers, and higher ferritin concentrations (corrected for inflammation) compared to children without inflammation or parasitaemia.** Similar results were found when infection was defined as clinical malaria or parasitaemia with/without fever (definitions 3 and 4). Conversely, when infection was defined using CRP only, all covariates were non-significant with the exception of baseline ferritin concentration. In Model 5, all infection definitions that included parasitaemia demonstrated a significant interaction between normalized difference vegetation index and land cover type. Maps of the predicted infection probabilities and spatial random effect showed defined high- and low-risk areas that tended to coincide with elevation and cluster around villages.

### CONCLUSIONS:

The risk of infection among young children in a malaria-endemic area may have a predictable spatial pattern which is associated with geographical characteristics, such as elevation and distance to a health facility.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4938940/>

## Malaria diagnosis

[Malar J.](#) 2017 Jan 3;16(1):6. doi: 10.1186/s12936-016-1658-y.

### Expanding access to parasite-based malaria diagnosis through retail drug shops in Tanzania: evidence from a randomized trial and implications for treatment.

[Maloney K](#)<sup>1</sup>, [Ward A](#)<sup>2</sup>, [Krenz B](#)<sup>3</sup>, [Petty N](#)<sup>1</sup>, [Bryson L](#)<sup>1</sup>, [Dolkart C](#)<sup>1</sup>, [Visser T](#)<sup>1</sup>, [Le Menach A](#)<sup>1</sup>, [Scott VK](#)<sup>1</sup>, [Cohen JM](#)<sup>1</sup>, [Mtumbuka E](#)<sup>3</sup>, [Mkude S](#)<sup>4</sup>.

### Abstract

#### BACKGROUND:

Tanzania has seen a reduction in the fraction of fevers caused by malaria, likely due in part to scale-up of control measures. While national guidelines require parasite-based diagnosis prior to treatment, it is estimated that more than half of suspected malaria treatment-seeking in Tanzania initiates in the private retail sector, where diagnosis by malaria rapid diagnostic test (RDT) or microscopy is illegal. This pilot study investigated whether the introduction of RDTs into Accredited Drug Dispensing Outlets (ADDOs) under realistic market conditions would improve case management practices.

#### METHODS:

Dispensers from ADDOs in two intervention districts in Tanzania were trained to stock and perform RDTs and monitored quarterly. Each district was assigned a different recommended retail price to evaluate the need for a subsidy. Malaria RDT and artemisinin-based combination therapy (ACT) uptake and availability were measured pre-intervention and 1 year post-



intervention through structured surveys of ADDO owners and exiting customers in both intervention districts and one contiguous control district. Descriptive analysis and logistic regression were used to compare the three districts and identify predictive variables for testing.

### RESULTS AND DISCUSSION:

**A total of 310 dispensers from 262 ADDOs were trained to stock and perform RDTs. RDT availability in intervention ADDOs increased from 1% (n = 172) to 73% (n = 163) during the study; ACT medicines were available in 75% of 260 pre-intervention and 68% of 254 post-intervention ADDOs.** Pre-treatment testing performed within the ADDO increased from 0 to 65% of suspected malaria patients who visited a shop (95% CI 60.8-69.6%) with no difference between intervention districts. Overall parasite-based diagnosis increased from 19 to 74% in intervention districts and from 3 to 18% in the control district. Prior knowledge of RDT availability (aOR = 1.9, p = 0.03) and RDT experience (aOR = 1.9, p = 0.01) were predictors for testing. Adherence data indicated that 75% of malaria positives received ACT, while 3% of negatives received ACT.

### CONCLUSIONS:

**Trained and supervised ADDO dispensers in rural Tanzania performed and sold RDTs under real market conditions to two-thirds of suspected malaria patients during this one-year pilot.** These results support the hypothesis that introducing RDTs into regulated private retail sector settings can improve malaria testing and treatment practices without an RDT subsidy.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209819/>

[Trop Med Int Health](#). 2016 Sep;21(9):1157-70. doi: 10.1111/tmi.12748. Epub 2016 Aug 9.  
[Appropriate targeting of artemisinin-based combination therapy by community health workers using malaria rapid diagnostic tests: findings from randomized trials in two contrasting areas of high and low malaria transmission in south-western Uganda.](#)  
[Ndyomugenyi R<sup>1</sup>](#), [Magnussen P<sup>2</sup>](#), [Lal S<sup>3</sup>](#), [Hansen K<sup>4</sup>](#), [Clarke SE<sup>3</sup>](#).

### OBJECTIVE:

To compare the impact of malaria rapid diagnostic tests (mRDTs), used by community health workers (CHWs), on the proportion of children <5 years of age receiving appropriately targeted treatment with artemisinin-based combination therapy (ACT), vs. presumptive treatment.

### METHODS:

Cluster-randomized trials were conducted in two contrasting areas of moderate-to-high and low malaria transmission in rural Uganda. Each trial examined the effectiveness of mRDTs in the management of malaria and targeting of ACTs by CHWs comparing two diagnostic approaches: **(i) presumptive clinical diagnosis of malaria [control arm] and (ii) confirmatory diagnosis with mRDTs followed by ACT treatment for positive patients [intervention arm], with village as the unit of randomisation.** Treatment decisions by CHWs were validated by microscopy on a reference blood slide collected at the time of consultation, to compare the proportion of children <5 years receiving appropriately targeted ACT treatment, defined as patients with microscopically-confirmed presence of parasites in a peripheral blood smear receiving artemether-lumefantrine or rectal artesunate, and patients with no malaria parasites not given ACT.

### RESULTS:

In the moderate-to-high transmission area, ACT treatment was appropriately targeted in 79.3% (520/656) of children seen by CHWs using mRDTs to diagnose malaria, vs. 30.8% (215/699) of children seen by CHWs using presumptive diagnosis (P < 0.001). In the low transmission area, 90.1% (363/403) children seen by CHWs using mRDTs received appropriately targeted ACT



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treatment vs. 7.8% (64/817) seen by CHWs using presumptive diagnosis ( $P < 0.001$ ). Low mRDT sensitivity in children with low-density parasitaemia ( $<200$  parasites/ $\mu$ l) was identified as a potential concern.

### CONCLUSION:

**When equipped with mRDTs, ACT treatments delivered by CHWs are more accurately targeted to children with malaria parasites.** mRDT use could play an important role in reducing overdiagnosis of malaria and improving fever case management within iCCM, in both moderate-to-high and low transmission areas. Nonetheless, missed treatments due to the low sensitivity of current mRDTs in patients with low parasite density are a concern. For community-based treatment in areas of low transmission and/or non-immune populations, presumptive treatment of all fevers as malaria may be advisable, until more sensitive diagnostic assays, suitable for routine use by CHWs in remote settings, become available.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5031222/>

[Malar J](#). 2016 Nov 24;15(1):568.

### Community health workers adherence to referral guidelines: evidence from studies introducing RDTs in two malaria transmission settings in Uganda.

[Lal S](#)<sup>1</sup>, [Ndyomugenyi R](#)<sup>2</sup>, [Paintain L](#)<sup>3</sup>, [Alexander ND](#)<sup>4</sup>, [Hansen KS](#)<sup>5</sup>, [Magnussen P](#)<sup>6</sup>, [Chandramohan D](#)<sup>3</sup>, [Clarke SE](#)<sup>3</sup>.

#### Abstract

#### BACKGROUND:

Many malaria-endemic countries have implemented national community health worker (CHW) programmes to serve remote populations that have poor access to malaria diagnosis and treatment. **Despite mounting evidence of CHWs' ability to adhere to malaria rapid diagnostic tests (RDTs) and treatment guidelines, there is limited evidence whether CHWs adhere to the referral guidelines and refer severely ill children for further management.** In southwest Uganda, this study examined whether CHWs referred children according to training guidelines and described factors associated with adherence to the referral guideline.

#### METHODS:

A secondary analysis was undertaken of data collected during two cluster-randomized trials conducted between January 2010 and July 2011, one in a moderate-to-high malaria transmission setting and the other in a low malaria transmission setting. **All CHWs were trained to prescribe artemisinin-based combination therapy (ACT) and recognize symptoms in children that required immediate referral to the nearest health centre.** Intervention arm CHWs had additional training on how to conduct an RDT; CHWs in the control arm used a presumptive diagnosis for malaria using clinical signs and symptoms. CHW treatment registers were reviewed to identify children eligible for referral according to training guidelines (temperature of  $\geq 38.5$  °C), to assess whether CHWs adhered to the guidelines and referred them. Factors associated with adherence were examined with logistic regression models.

#### RESULTS:

**CHWs failed to refer 58.8% of children eligible in the moderate-to-high transmission and 31.2% of children in the low transmission setting.** CHWs using RDTs adhered to the referral guidelines more frequently than CHWs not using RDTs (moderate-to-high transmission: 50.1 vs 18.0%,  $p = 0.003$ ; low transmission: 88.5 vs 44.1%,  $p < 0.001$ ). In both settings, fewer than 20% of eligible children received pre-referral treatment with rectal artesunate. Children who were prescribed ACT were very unlikely to be referred in both settings (97.7 and 73.3% were not referred in the moderate-to-high and low transmission settings, respectively). In the moderate-

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to-high transmission setting, day and season of visit were also associated with the likelihood of adherence to the referral guidelines, but not in the low transmission setting.

### CONCLUSIONS:

CHW adherence to referral guidelines was poor in both transmission settings. However, training CHWs to use RDT improved correct referral of children with a high fever compared to a presumptive diagnosis using sign and symptoms. As many countries scale up CHW programmes, routine monitoring of reported data should be examined carefully to assess whether CHWs adhere to referral guidelines and take remedial actions where required.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5121932/>

## Insecticide-treated bed nets

[Malar J](#). 2017 Apr 7;16(1):142. doi: 10.1186/s12936-017-1767-2.

### **Effects of community-level bed net coverage on malaria morbidity in Lilongwe, Malawi.**

[Escamilla V](#)<sup>1</sup>, [Alker A](#)<sup>2</sup>, [Dandalo L](#)<sup>3</sup>, [Juliano JJ](#)<sup>2,4,5</sup>, [Miller WC](#)<sup>2,4</sup>, [Kamthuya P](#)<sup>3</sup>, [Tembo T](#)<sup>3</sup>, [Tegha G](#)<sup>3</sup>, [Martinson F](#)<sup>3</sup>, [Emch M](#)<sup>4,6</sup>, [Hoffman IF](#)<sup>2,3</sup>.

### BACKGROUND:

The protective effect of insecticide-treated bed nets against individual-level malaria transmission is well known, however community-level effects are less understood. **Protective effects from community-level bed net use against malaria transmission have been observed in clinical trials, however, the relationship is less clear outside of a controlled research setting.** The objective of this research was to investigate the effect of community-level bed net use against malaria transmission outside of a bed net clinical trial setting in Lilongwe, Malawi following national efforts to scale-up ownership of long-lasting, insecticide-treated bed nets.

### METHODS:

An annual, cross-sectional, household-randomized, malaria transmission intensity survey was conducted in Lilongwe, Malawi (2011-2013). Health, demographic, and geographic-location data were collected. Participant blood samples were tested for *Plasmodium falciparum* presence. The percentage of people sleeping under a bed net within 400-m and 1-km radii of all participants was measured. Mixed effects logistic regression models were used to measure the relationship between malaria prevalence and surrounding bed net coverage. Each year, 800 people were enrolled (400 <5 years; 200 5-19 years; 200 ≥20 years; total n = 2400).

### RESULTS:

**From 2011 to 2013, malaria prevalence declined from 12.9 to 5.6%, while bed net use increased from 53.8 to 78.6%. For every 1% increase in community bed net coverage, malaria prevalence decreased among children under 5 years old** [adjusted odds ratio: 0.98 (0.96, 1.00)]. Similar effects were observed in participants 5-19 years [unadjusted odds ratio: 0.98 (0.97, 1.00)]; the effect was attenuated after adjusting for individual-level bed net use. Community coverage was not associated with malaria prevalence among adults ≥20 years. Supplemental analyses identified more pronounced indirect protective effects from community-level bed net use against malaria transmission among children under 5 years who were sleeping under a bed net [adjusted odds ratio: 0.97 (0.94, 0.99)], compared to children who were not sleeping under a bed net [adjusted odds ratio: 0.99 (0.97, 1.01)].

### CONCLUSIONS:

**Malawi's efforts to scale up ownership of long-lasting, insecticide-treated bed nets are effective in increasing reported use.** Increased community-level bed net coverage appears to provide additional protection against malaria transmission beyond individual use in a real-world context.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5383956/>

[Malar J](#). 2017 Jan 3;16(1):12. doi: 10.1186/s12936-016-1654-2.

**The effect of small solar powered 'Bɔkɔɔ' net fans on mosquito net use: results from a randomized controlled cross-over trial in southern Ghana.**

[Briët OJ](#)<sup>1,2</sup>, [Yukich JO](#)<sup>3,4</sup>, [Pfeiffer C](#)<sup>5,6</sup>, [Miller W](#)<sup>7</sup>, [Jaeger MS](#)<sup>5,6</sup>, [Khanna N](#)<sup>5,6</sup>, [Oppong S](#)<sup>8</sup>, [Nardini P](#)<sup>7</sup>, [Ahorlu CK](#)<sup>9</sup>, [Keating J](#)<sup>3,4</sup>.

**BACKGROUND:**

Long-lasting insecticidal nets (LLINs) are ineffective malaria transmission prevention tools if they are unused. Discomfort due to heat is the most commonly reported reason for not using nets, but this problem is largely unaddressed. With increasing rural electrification and the dropping price of solar power, fans could improve comfort inside nets and be affordable to populations in malaria endemic areas. Here, results are presented from a pilot randomized controlled cross-over study testing the effect of fans on LLIN use.

**METHODS:**

Eighty-three households from two rural communities in Greater Accra, Ghana, randomized into three groups, participated in a 10-month cross-over trial. After a screening survey to identify eligible households, all households received new LLINs. **Bɔkɔɔ net fan systems (one fan per member) were given to households in Group 1 and water filters were given to households in Group 2.** At mid-point, Group 1 and 2 crossed over interventions. Households in Group 1 and 2 participated in fortnightly surveys on households' practices related to nets, fans and water filters, while households in Group 3 were surveyed only at screening, mid-point and study end. Entomological and weather data were collected throughout the study. Analysis took both 'per protocol' (PP) and 'intention to treat' (ITT) approaches. The mid- and end-point survey data from Group 1 and 2 were analysed using Firth logistic regressions. Fortnightly survey data from all groups were analysed using logistic regressions with random effects.

**RESULTS:**

**Provision of fans to households appeared to increase net use in this study.** Although the increase in net use explained by fans was not significant in the primary analyses (ITT odds ratio 3.24,  $p > 0.01$ ; PP odds ratio = 1.17,  $p > 0.01$ ), it was significant in secondary PP analysis (odds ratio = 1.95,  $p < 0.01$ ). Net use was high at screening and even higher after provision of new LLINs and with follow up. Fan use was 90-100% depending on the fortnightly visit.

**CONCLUSIONS:**

This pilot study could not provide definitive evidence that fans increase net use. A larger study with additional statistical power is needed to assess this association across communities with diverse environmental and socio-demographic characteristics.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209841/>

[Lancet Infect Dis](#). 2016 Oct;16(10):1169-77. doi: 10.1016/S1473-3099(16)30148-7. Epub 2016 Jun 29.

**Efficacy of topical mosquito repellent (picaridin) plus long-lasting insecticidal nets versus long-lasting insecticidal nets alone for control of malaria: a cluster randomised controlled trial.**

[Sluydts V](#)<sup>1</sup>, [Durnez L](#)<sup>2</sup>, [Heng S](#)<sup>3</sup>, [Gryseels C](#)<sup>4</sup>, [Canier L](#)<sup>5</sup>, [Kim S](#)<sup>5</sup>, [Van Roey K](#)<sup>2</sup>, [Kerkhof K](#)<sup>2</sup>, [Khim N](#)<sup>5</sup>, [Mao S](#)<sup>6</sup>, [Uk S](#)<sup>6</sup>, [Sovannaroeth S](#)<sup>6</sup>, [Grietens KP](#)<sup>7</sup>, [Sochantha T](#)<sup>6</sup>, [Menard D](#)<sup>5</sup>, [Coosemans M](#)<sup>8</sup>.

## BACKGROUND:

Although effective topical repellents provide personal protection against malaria, **whether mass use of topical repellents in addition to long-lasting insecticidal nets can contribute to a further decline of malaria is not known**, particularly in areas where outdoor transmission occurs. We aimed to assess the epidemiological efficacy of a highly effective topical repellent in addition to long-lasting insecticidal nets in reducing malaria prevalence in this setting.

## METHODS:

**A cluster randomised controlled trial was done in the 117 most endemic villages in Ratanakiri province, Cambodia, to assess the efficacy of topical repellents in addition to long-lasting insecticidal nets in controlling malaria in a low-endemic setting.** We did a pre-trial assessment of village accessibility and excluded four villages because of their inaccessibility during the rainy season. Another 25 villages were grouped because of their proximity to each other, resulting in 98 study clusters (comprising either a single village or multiple neighbouring villages). Clusters were randomly assigned (1:1) to either a control (long-lasting insecticidal nets) or intervention (long-lasting insecticidal nets plus topical repellent) study group after a restricted randomisation. **All clusters received one long-lasting insecticidal net per individual, whereas those in the intervention group also received safe and effective topical repellents** (picaridin KBR3023, SC Johnson, Racine, WI, USA), along with instruction and promotion of its daily use. Cross-sectional surveys of 65 randomly selected individuals per cluster were done at the beginning and end of the malaria transmission season in 2012 and 2013. The primary outcome was Plasmodium species-specific prevalence in participants obtained by real-time PCR, assessed in the intention-to-treat population. Complete safety analysis data will be published separately; any ad-hoc adverse events are reported here. This trial is registered with ClinicalTrials.gov, number [NCT01663831](#).

## FINDINGS:

Of the 98 clusters that villages were split into, 49 were assigned to the control group and 49 were assigned to the intervention group. Despite having a successful distribution system, the daily use of repellents was suboptimum. **No post-intervention differences in PCR plasmodium prevalence were observed between study groups** in 2012 (4.91% in the control group vs 4.86% in the intervention group; adjusted odds ratio [aOR] 1.01 [95% CI 0.60-1.70];  $p=0.975$ ) or in 2013 (2.96% in the control group vs 3.85% in the intervention group; aOR 1.31 [0.81-2.11];  $p=0.266$ ). Similar results were obtained according to Plasmodium species (1.33% of participants in the intervention group vs 1.10% in the intervention group were infected with Plasmodium falciparum; aOR 0.83 [0.44-1.56];  $p=0.561$ ; and 1.85% in the control group vs 2.67% in the intervention group were infected with Plasmodium vivax; aOR 1.51 [0.88-2.57];  $p=0.133$ ). 41 adverse event notifications from nine villages were received, of which 33 were classified as adverse reactions (11 of these 33 were cases of repellent abuse through oral ingestion, either accidental or not). All participants with adverse reactions fully recovered and 17 were advised to permanently stop using the repellent.

## INTERPRETATION:

**Mass distribution of highly effective topical repellents in resource-sufficient conditions did not contribute to a further decline in malaria endemicity in a pre-elimination setting in the Greater Mekong subregion.** Daily compliance and appropriate use of the repellents remains the main obstacle.

Free access: [http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(16\)30148-7/fulltext](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30148-7/fulltext)

Malar J. 2016 Oct 18;15(1):509.

**Communication for behavioural impact in enhancing utilization of insecticide-treated bed nets among mothers of under-five children in rural North Sudan: an experimental study.**

Elmosaad YM<sup>1</sup>, Elhadi M<sup>2</sup>, Khan A<sup>3</sup>, Malik EM<sup>4</sup>, Mahmud I<sup>3,5</sup>.

**BACKGROUND:**

Malaria is the leading cause of morbidity and mortality in Sudan. The entire population is at risk of contracting malaria to different levels. **This study aimed to assess the effectiveness of communication for behavioural impact (COMBI) strategy in enhancing the utilization of long-lasting insecticidal nets (LLINs) among mothers of under-five children in rural areas.**

**METHODS:**

A randomized community trial was conducted in rural area of Kosti locality, White Nile State, Sudan, among mothers of under-five children, from January 2013 to February 2014. A total of **761 mothers from 12 villages were randomly selected, 412 mothers from intervention villages and 349 were from comparison villages.**

**RESULTS:**

**The knowledge of mothers, in intervention villages, about malaria vector, personal protective measures (PPM) against malaria, and efficacy of LLINs was significantly increased from 86.9 to 97.3 %; 45.9 to 92 % and 77.7 to 96.1 % respectively.** Knowledge about usefulness of PPM, types of mosquito nets and efficacy of LLINs was significantly higher in intervention villages compared to comparison villages ( $p < 0.05$ ), ( $\eta^2 = 0.64$ ). Mothers in intervention villages increasingly perceived, post-intervention, that malaria was a serious disease (99.3 %), a preventable disease (98.8 %) and also LLINs as an effective intervention in malaria prevention (92.2 %). This resulted in an increase in the utilization rate of LLINs from 19.2 to 82.8 % in intervention villages compared to comparison villages ( $p < 0.05$ ) [OR = 4.6, 95 %, CI = (3.72-5.72)], ( $\eta^2 = 0.64$ ). The average of mothers' knowledge about malaria was increased by 64 % ( $\eta^2 = 0.64$ ), the use of LLINs was increased by 79 % ( $\eta^2 = 0.79$ ) and a positive attitude towards malaria was 2.25 times higher in intervention villages than among mothers in the comparison villages.

**CONCLUSIONS:**

These results established the usefulness of COMBI strategy for increasing awareness about malaria, developing a positive perception towards malaria prevention and, increasing the utilization of LLINs.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070147/>

BMC Public Health. 2016 Jul 25;16:633. doi: 10.1186/s12889-016-3287-3.

**The effectiveness of non-pyrethroid insecticide-treated durable wall lining to control malaria in rural Tanzania: study protocol for a two-armed cluster randomized trial.**

Mtove G<sup>1</sup>, Mugasa JP<sup>2</sup>, Messenger LA<sup>3</sup>, Malima RC<sup>2</sup>, Mangesho P<sup>2</sup>, Magogo F<sup>2</sup>, Plucinski M<sup>4,5</sup>, Hashimu R<sup>2</sup>, Matowo J<sup>6</sup>, Shepard D<sup>7</sup>, Batengana B<sup>2</sup>, Cook J<sup>3</sup>, Emidi B<sup>6,7</sup>, Halasa Y<sup>8</sup>, Kaaya R<sup>6</sup>, Kihombo A<sup>2</sup>, Lindblade KA<sup>5</sup>, Makenga G<sup>2</sup>, Mpangala R<sup>2</sup>, Mwambuli A<sup>2</sup>, Mzava R<sup>2</sup>, Mziray A<sup>2</sup>, Olang G<sup>2</sup>, Oxborough RM<sup>9</sup>, Seif M<sup>2</sup>, Sambu E<sup>2</sup>, Samuels A<sup>5</sup>, Sudi W<sup>2</sup>, Thomas J<sup>10</sup>, Weston S<sup>3</sup>, Alilio M<sup>11</sup>, Binkin N<sup>12</sup>, Gimnig J<sup>5</sup>, Kleinschmidt I<sup>3</sup>, McElroy P<sup>4,5</sup>, Moulton LH<sup>13</sup>, Norris L<sup>11</sup>, Ruebush T<sup>12</sup>, Venkatesan M<sup>11</sup>, Rowland M<sup>3</sup>, Mosha FW<sup>6</sup>, Kisinza WN<sup>2</sup>.

**Abstract**

**BACKGROUND:**



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Despite considerable reductions in malaria achieved by scaling-up long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), maintaining sustained community protection remains operationally challenging. Increasing insecticide resistance also threatens to jeopardize the future of both strategies. **Non-pyrethroid insecticide-treated wall lining (ITWL) may represent an alternate or complementary control method and a potential tool to manage insecticide resistance.** To date no study has demonstrated whether ITWL can reduce malaria transmission nor provide additional protection beyond the current best practice of universal coverage (UC) of LLINs and prompt case management.

### **METHODS/DESIGN:**

A two-arm cluster randomized controlled trial will be conducted in rural Tanzania to assess whether non-pyrethroid ITWL and UC of LLINs provide added protection against malaria infection in children, compared to UC of LLINs alone. Stratified randomization based on malaria prevalence will be used to select 22 village clusters per arm. All 44 clusters will receive LLINs and half will also have ITWL installed on interior house walls. Study children, aged 6 months to 11 years old, will be enrolled from each cluster and followed monthly to estimate cumulative incidence of malaria parasitaemia (primary endpoint), time to first malaria episode and prevalence of anaemia before and after intervention. Entomological inoculation rate will be estimated using indoor CDC light traps and outdoor tent traps followed by detection of *Anopheles gambiae* species, sporozoite infection, insecticide resistance and blood meal source. ITWL bioefficacy and durability will be monitored using WHO cone bioassays and household surveys, respectively. Social and cultural factors influencing community and household ITWL acceptability will be explored through focus-group discussions and in-depth interviews. Cost-effectiveness, compared between study arms, will be estimated per malaria case averted.

### **DISCUSSION:**

This protocol describes the large-scale evaluation of a novel vector control product, designed to overcome some of the known limitations of existing methods. If ITWL is proven to be effective and durable under field conditions, it may warrant consideration for programmatic implementation, particularly in areas with long transmission seasons and where pyrethroid-resistant vectors predominate. Trial findings will provide crucial information for policy makers in Tanzania and other malaria-endemic countries to guide resource allocations for future control efforts.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4960851/>

## Other preventative interventions

(See also: Vaccines – malaria vaccine)

[Int J Antimicrob Agents](#). 2017 Mar;49(3):339-347. doi: 10.1016/j.ijantimicag.2016.11.017. Epub 2017 Jan 17.

**Efficacy and safety of intermittent preventive treatment in schoolchildren with sulfadoxine/pyrimethamine (SP) and SP plus piperazine in Democratic Republic of the Congo: a randomised controlled trial.**

[Matangila JR](#)<sup>1</sup>, [Doua JY](#)<sup>2</sup>, [Mitashi P](#)<sup>3</sup>, [da Luz RI](#)<sup>2</sup>, [Lutumba P](#)<sup>3</sup>, [Van Geertruyden JP](#)<sup>2</sup>.

### **Abstract**

In endemic areas, malaria and its adverse effects in schoolchildren may be prevented by intermittent preventive treatment (IPTsc). However, the most appropriate drug regimen for IPTsc remains to be identified. A randomised controlled trial was conducted in Kinshasa, DRC.

**Enrolled schoolchildren were assigned to a passive control arm (n = 212), sulfadoxine/pyrimethamine (SP) (n = 202) or SP plus piperazine (SP/PQ) (n = 202). The**



primary endpoint was haemoglobin (Hb) change. Secondary endpoints were anaemia, parasitaemia prevalence and clinical malaria incidence. Data were analysed by modified intention-to-treat (mITT) and per-protocol. A linear mixed mode was used due to repeated measurements. Of 616 enrolled children, 410 (66.6%) were eligible for mITT analysis. The control arm was used as reference. After 12 months, the Hb level increased by 0.20 g/dL (95% CI -0.61 to 0.47;  $P = 0.168$ ) and 0.39 g/dL (0.12-0.66;  $P < 0.01$ ) in the SP and SP/PQ arms, respectively. **SP treatment reduced anaemia, malaria parasitaemia and clinical malaria by 10% (0-20%;  $P = 0.06$ ), 19% (2-33%;  $P = 0.042$ ) and 25% (-32 to 57%;  $P = 0.37$ ), respectively. The corresponding values for SP/PQ were 28% (19-37%;  $P < 0.001$ ), 40% (26-52%;  $P < 0.001$ ) and 58% (17-79%;  $P < 0.01$ ).** No deaths or severe adverse events (SAEs) were observed. **SP/PQ offered substantial protection against anaemia, malaria parasitaemia and clinical malaria and showed no SAEs. SP/PQ, a combination of two long-acting non-artemisinin-based antimalarials, may be a valuable option for IPTsc in Africa.**

[PLoS One](#). 2016 Oct 20;11(10):e0162563. doi: 10.1371/journal.pone.0162563. eCollection 2016.

**Safety of Seasonal Malaria Chemoprevention (SMC) with Sulfadoxine-Pyrimethamine plus Amodiaquine when Delivered to Children under 10 Years of Age by District Health Services in Senegal: Results from a Stepped-Wedge Cluster Randomized Trial.**

[NDiaye JL](#)<sup>1</sup>, [Cissé B](#)<sup>1,2</sup>, [Ba EH](#)<sup>3</sup>, [Gomis JF](#)<sup>3</sup>, [Ndour CT](#)<sup>1</sup>, [Molez JF](#)<sup>3</sup>, [Fall FB](#)<sup>4</sup>, [Sokhna C](#)<sup>3</sup>, [Faye B](#)<sup>1</sup>, [Kouevijdin E](#)<sup>3</sup>, [Niane FK](#)<sup>1</sup>, [Cairns M](#)<sup>5</sup>, [Trape JF](#)<sup>3</sup>, [Rogier C](#)<sup>2</sup>, [Gaye O](#)<sup>1</sup>, [Greenwood BM](#)<sup>5</sup>, [Milligan PJ](#)<sup>5</sup>.

**Abstract**

**BACKGROUND:**

It is recommended that children aged 3 months to five years of age living in areas of seasonal transmission in the sub-Saharan should receive Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) during the malaria transmission season. The purpose of this study was to evaluate the safety of SMC with SPAQ in children when delivered by community health workers in three districts in Senegal where SMC was introduced over three years, in children from 3 months of age to five years of age in the first year, then in children up to 10 years of age.

**METHODS:**

A surveillance system was established to record all deaths and all malaria cases diagnosed at health facilities and a pharmacovigilance system was established to detect adverse drug reactions. Health posts were randomized to introduce SMC in a stepped wedge design. SMC with SPAQ was administered once per month from September to November, by nine health-posts in 2008, by 27 in 2009 and by 45 in 2010.

**RESULTS:**

After three years, 780,000 documented courses of SMC had been administered. High coverage was achieved. No serious adverse events attributable to the intervention were detected, despite a high level of surveillance.

**CONCLUSIONS:**

SMC is being implemented in countries of the sub-Saharan for children under 5 years of age, but in some areas the age distribution of cases of malaria may justify extending this age limit, as has been done in Senegal. Our results show that SMC is well tolerated in children under five and in older children. However, pharmacovigilance should be maintained where SMC is implemented and provision for strengthening national pharmacovigilance systems should be included in plans for SMC implementation.

[PLoS Med.](#) 2016 Nov 22;13(11):e1002175. doi: 10.1371/journal.pmed.1002175. eCollection 2016 Nov.

**Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial.**

[Cissé B](#)<sup>1,2</sup>, [Ba EH](#)<sup>2,3</sup>, [Sokhna C](#)<sup>3</sup>, [NDiaye JL](#)<sup>1</sup>, [Gomis JF](#)<sup>1</sup>, [Dial Y](#)<sup>4</sup>, [Pitt C](#)<sup>2</sup>, [NDiaye M](#)<sup>1</sup>, [Cairns M](#)<sup>2</sup>, [Faye E](#)<sup>1</sup>, [NDiaye M](#)<sup>1</sup>, [Lo A](#)<sup>1</sup>, [Tine R](#)<sup>1</sup>, [Faye S](#)<sup>1</sup>, [Faye B](#)<sup>1</sup>, [Sy O](#)<sup>1</sup>, [Konate L](#)<sup>1</sup>, [Kouevijdin E](#)<sup>3</sup>, [Flach C](#)<sup>2</sup>, [Faye O](#)<sup>1</sup>, [Trape JF](#)<sup>3</sup>, [Sutherland C](#)<sup>2</sup>, [Fall FB](#)<sup>4</sup>, [Thior PM](#)<sup>4</sup>, [Faye OK](#)<sup>4</sup>, [Greenwood B](#)<sup>2</sup>, [Gaye O](#)<sup>1</sup>, [Milligan P](#)<sup>2</sup>.

**BACKGROUND:**

Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ), given each month during the transmission season, is recommended for children living in areas of the Sahel where malaria transmission is highly seasonal. The recommendation for SMC is currently limited to children under five years of age, but, in many areas of seasonal transmission, the burden in older children may justify extending this age limit. This study was done to determine the effectiveness of SMC in Senegalese children up to ten years of age.

**METHODS AND FINDINGS:**

SMC was introduced into three districts over three years in central Senegal using a stepped-wedge cluster-randomised design. A census of the population was undertaken and a surveillance system was established to record all deaths and to record all cases of malaria seen at health facilities. A pharmacovigilance system was put in place to detect adverse drug reactions. Fifty-four health posts were randomised. Nine started implementation of SMC in 2008, 18 in 2009, and a further 18 in 2010, with 9 remaining as controls. In the first year of implementation, SMC was delivered to children aged 3-59 months; the age range was then extended for the latter two years of the study to include children up to 10 years of age. Cluster sample surveys at the end of each transmission season were done to measure coverage of SMC and the prevalence of parasitaemia and anaemia, to monitor molecular markers of drug resistance, and to measure insecticide-treated net (ITN) use. Entomological monitoring and assessment of costs of delivery in each health post and of community attitudes to SMC were also undertaken. About 780,000 treatments were administered over three years. Coverage exceeded 80% each month. Mortality, the primary endpoint, was similar in SMC and control areas (4.6 and 4.5 per 1000 respectively in children under 5 years and 1.3 and 1.2 per 1000 in children 5-9 years of age; the overall mortality rate ratio [SMC: no SMC] was 0.90, 95% CI 0.68-1.2,  $p = 0.496$ ). **A reduction of 60% (95% CI 54%-64%,  $p < 0.001$ ) in the incidence of malaria cases confirmed by a rapid diagnostic test (RDT) and a reduction of 69% (95% CI 65%-72%,  $p < 0.001$ ) in the number of treatments for malaria (confirmed and unconfirmed) was observed in children.** In areas where SMC was implemented, incidence of confirmed malaria in adults and in children too old to receive SMC was reduced by 26% (95% CI 18%-33%,  $p < 0.001$ ) and the total number of treatments for malaria (confirmed and unconfirmed) in these older age groups was reduced by 29% (95% CI 21%-35%,  $p < 0.001$ ). One hundred and twenty-three children were admitted to hospital with a diagnosis of severe malaria, with 64 in control areas and 59 in SMC areas, showing a reduction in the incidence rate of severe disease of 45% (95% CI 5%-68%,  $p = 0.031$ ). Estimates of the reduction in the prevalence of parasitaemia at the end of the transmission season in SMC areas were 68% (95% CI 35%-85%)  $p = 0.002$  in 2008, 84% (95% CI 58%-94%,  $p < 0.001$ ) in 2009, and 30% (95% CI -130%-79%,  $p = 0.56$ ) in 2010. SMC was well tolerated with no serious adverse reactions attributable to SMC drugs. Vomiting was the most commonly reported mild adverse event but was reported in less than 1% of treatments. The

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average cost of delivery was US\$0.50 per child per month, but varied widely depending on the size of the health post. Limitations included the low rate of mortality, which limited our ability to detect an effect on this endpoint.

### CONCLUSIONS:

**SMC substantially reduced the incidence of outpatient cases of malaria and of severe malaria in children, but no difference in all-cause mortality was observed.** Introduction of SMC was associated with an overall reduction in malaria incidence in untreated age groups. In many areas of Africa with seasonal malaria, there is a substantial burden in older children that could be prevented by SMC. SMC in older children is well tolerated and effective and can contribute to reducing malaria transmission.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5119693/>

[Antimicrob Agents Chemother.](#) 2016 Sep 23;60(10):5649-54. doi: 10.1128/AAC.00920-16. Print 2016 Oct.

### Intermittent Preventive Treatment with Dihydroartemisinin-Piperaquine in Ugandan Schoolchildren Selects for Plasmodium falciparum Transporter Polymorphisms That Modify Drug Sensitivity.

[Nankabirwa JI](#)<sup>1</sup>, [Conrad MD](#)<sup>2</sup>, [Legac J](#)<sup>2</sup>, [Tukwasibwe S](#)<sup>3</sup>, [Tumwebaze P](#)<sup>3</sup>, [Wandera B](#)<sup>4</sup>, [Brooker SJ](#)<sup>5</sup>, [Staedke SG](#)<sup>6</sup>, [Kamya MR](#)<sup>7</sup>, [Nsobya SL](#)<sup>3</sup>, [Dorsey G](#)<sup>2</sup>, [Rosenthal PJ](#)<sup>2</sup>.

#### Abstract

Dihydroartemisinin-piperaquine (DP) offers prolonged protection against malaria, but its impact on Plasmodium falciparum drug sensitivity is uncertain. **In a trial of intermittent preventive treatment in schoolchildren in Tororo, Uganda, in 2011 to 2012, monthly DP for 1 year decreased the incidence of malaria by 96% compared to placebo; DP once per school term offered protection primarily during the first month after therapy. To assess the impact of DP on selection of drug resistance, we compared the prevalence of key polymorphisms in isolates that emerged at different intervals after treatment with DP.** Blood obtained monthly and at each episode of fever was assessed for P. falciparum parasitemia by microscopy. Samples from 160 symptomatic and 650 asymptomatic episodes of parasitemia were assessed at 4 loci (N86Y, Y184F, and D1246Y in pfmdr1 and K76T in pfert) that modulate sensitivity to aminoquinoline antimalarials, utilizing a ligase detection reaction-fluorescent microsphere assay. **For pfmdr1 N86Y and pfert K76T, but not the other studied polymorphisms, the prevalences of mutant genotypes were significantly greater in children who had received DP within the past 30 days than in those not treated within 60 days (86Y, 18.0% versus 8.3% [P = 0.03]; 76T, 96.0% versus 86.1% [P = 0.05]), suggesting selective pressure of DP.** Full sequencing of pfert in a subset of samples did not identify additional polymorphisms selected by DP. **In summary, parasites that emerged soon after treatment with DP were more likely than parasites not under drug pressure to harbor pfmdr1 and pfert polymorphisms associated with decreased sensitivity to aminoquinoline antimalarials.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5038325/>

[J Infect Dis.](#) 2016 Dec 15;214(12):1831-1839.

### Short-term Impact of Mass Drug Administration With Dihydroartemisinin Plus Piperaquine on Malaria in Southern Province Zambia: A Cluster-Randomized Controlled Trial.

## Randomised trials in child health in developing countries 2016-17

[Eisele TP](#)<sup>1</sup>, [Bennett A](#)<sup>2</sup>, [Silumbe K](#)<sup>3</sup>, [Finn TP](#)<sup>1</sup>, [Chalwe V](#)<sup>4</sup>, [Kamuliwo M](#)<sup>5</sup>, [Hamainza B](#)<sup>5</sup>, [Moonga H](#)<sup>5</sup>, [Kooma E](#)<sup>6</sup>, [Chizema Kawesha E](#)<sup>5</sup>, [Yukich J](#)<sup>1</sup>, [Keating J](#)<sup>1</sup>, [Porter T](#)<sup>1</sup>, [Conner RO](#)<sup>7</sup>, [Earle D](#)<sup>3</sup>, [Steketee RW](#)<sup>7</sup>, [Miller JM](#)<sup>3</sup>.

### BACKGROUND:

Mass drug administration (MDA) using dihydroartemisinin plus piperaquine (DHAp) represents a potential strategy to clear *Plasmodium falciparum* infections and reduce the human parasite reservoir.

### METHODS:

A cluster-randomized controlled trial in Southern Province, Zambia, was used to assess the short-term impact of 2 rounds of community-wide MDA and household-level (focal) MDA with DHAp compared with no mass treatment. Study end points included parasite prevalence in children, infection incidence, and confirmed malaria case incidence.

### RESULTS:

All end points significantly decreased after intervention, irrespective of treatment group. Parasite prevalence from 7.71% at baseline to 0.54% after MDA in lower-transmission areas, resulting in an 87% reduction compared with control (adjusted odds ratio, 0.13; 95% confidence interval, .02-.92;  $P = .04$ ). No difference between treatment groups was observed in areas of high transmission. The 5-month cumulative infection incidence was 70% lower (crude incidence rate ratio, 0.30; 95% confidence interval, .06-1.49;  $P = .14$ ) and 58% lower (0.42; .18-.98;  $P = .046$ ) after MDA compared with control in lower- and higher-transmission areas, respectively. No significant impact of focal MDA was observed for any end point.

### CONCLUSIONS:

Two rounds of MDA with DHAp rapidly reduced infection prevalence, infection incidence, and confirmed case incidence rates, especially in low-transmission areas.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142084/>

[EBioMedicine](#). 2016 Nov;13:348-355. doi: 10.1016/j.ebiom.2016.10.032. Epub 2016 Oct 23.

### [The Gametocytocidal Efficacy of Different Single Doses of Primaquine with Dihydroartemisinin-piperaquine in Asymptomatic Parasite Carriers in The Gambia: A Randomized Controlled Trial.](#)

[Okebe J](#)<sup>1</sup>, [Bousema T](#)<sup>2</sup>, [Affara M](#)<sup>3</sup>, [Di Tanna GL](#)<sup>4</sup>, [Dabira E](#)<sup>5</sup>, [Gaye A](#)<sup>6</sup>, [Sanya-Isijola F](#)<sup>7</sup>, [Badji H](#)<sup>8</sup>, [Correa S](#)<sup>9</sup>, [Nwakanma D](#)<sup>10</sup>, [Van Geertruyden JP](#)<sup>11</sup>, [Drakeley C](#)<sup>12</sup>, [D'Alessandro U](#)<sup>13</sup>.

### BACKGROUND:

Asymptomatic low-density gametocyte carriers represent the majority of malaria-infected individuals. However, the impact of recommended treatment with single low dose of primaquine and an artemisinin-based combination therapy to reduce transmission in this group is unknown.

### METHODS:

This was a four-arm, open label, randomized controlled trial comparing the effect of dihydroartemisinin-piperaquine (DHAP) alone or combined with single dose of primaquine (PQ) at 0.20mg/kg, 0.40mg/kg, or 0.75mg/kg on *Plasmodium falciparum* gametocytaemia, infectiousness to mosquitoes and hemoglobin change in asymptomatic, malaria-infected, glucose-6-phosphate dehydrogenase (G6PD) normal individuals.

Randomization was done using a computer-generated sequence of uneven block sizes with codes concealed in sequentially numbered opaque envelopes. The primary endpoint was the prevalence of *P. falciparum* gametocytemia at day 7 of follow-up determined by quantitative nucleic acid sequence based assay and analysis was by intention to treat. The trial has been concluded (registration number: [NCT01838902](#);

### RESULTS:

**A total of 694 asymptomatic, malaria-infected individuals were enrolled.** Gametocyte prevalence at day 7 was 37.0% (54/146; 95% CI 29.2-45.4), 19.0% (27/142; 95% CI 12.9-26.4), 17.2% (25/145; 95% CI 11.0-23.5) and 10.6% (15/141; 95% CI 6.1-16.9) in the DHAP alone, 0.20mg/kg, 0.40mg/kg, and 0.75mg/kg PQ arms, respectively. The main adverse events reported include headache (130/471, 27.6%), cough (73/471, 15.5%), history of fever (61/471, 13.0%) and abdominal pain (57/471, 12.1%). There were five serious adverse events however, none was related to the interventions.

### INTERPRETATION:

**A single course of PQ significantly reduces gametocyte carriage in malaria-infected asymptomatic, G6PD-normal individuals without increasing the risk of clinical anemia.** The limited number of successful mosquito infections suggests that post-treatment transmission potential in this asymptomatic population is low.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5264436/>

[Malar J](#). 2016 Jul 22;15(1):378. doi: 10.1186/s12936-016-1433-0.

### **A cluster randomized trial comparing deltamethrin and bendiocarb as insecticides for indoor residual spraying to control malaria on Bioko Island, Equatorial Guinea.**

[Bradley J](#)<sup>1</sup>, [Hergott D](#)<sup>2</sup>, [Garcia G](#)<sup>2</sup>, [Lines J](#)<sup>3</sup>, [Cook J](#)<sup>4</sup>, [Slotman MA](#)<sup>5</sup>, [Phiri WP](#)<sup>2</sup>, [Schwabe C](#)<sup>2</sup>, [Kleinschmidt I](#)<sup>4,6</sup>.

### Abstract

#### BACKGROUND:

Indoor residual spraying (IRS) has been used on Bioko for malaria control since 2004. In 2013 the insecticide was changed from bendiocarb to deltamethrin. Shortly after this change, there was a marked increase in malaria prevalence on the island. This trial was carried out to compare the effectiveness of bendiocarb and deltamethrin for use in IRS on Bioko.

#### METHODS:

**Twenty-four clusters of houses were randomized to receive IRS with either bendiocarb or deltamethrin.** Approximately 3 months after the intervention, the prevalence of malaria and levels of haemoglobin were measured in children aged 2-14 years in each cluster.

#### RESULTS:

**Prevalence of malaria in 2-14 year olds was lower in the bendiocarb arm (16.8, 95 % CI 11.1-24.7, N = 1374) than in the deltamethrin arm (23.2, 95 % CI 16.0-32.3, N = 1330) but this difference was not significant (p = 0.390), even after adjusting for covariates (p = 0.119).** Mean haemoglobin in children was marginally higher in the bendiocarb clusters (11.6 g/dl, 95 % CI 11.5-11.8, N = 1326) than in the deltamethrin clusters (11.5 g/dl, 95 % CI 11.3-11.7, N = 1329). This difference was borderline significant after adjusting for covariates (p = 0.049).

#### CONCLUSIONS:

The results are suggestive of bendiocarb being more effective at preventing malaria on Bioko although evidence for this was weak. The results are likely due to the fact that local vectors remain fully susceptible to bendiocarb whereas subsequent tests have shown resistance to deltamethrin.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957409/>



**Geographical patterns of malaria transmission based on serological markers for falciparum and vivax malaria in Ratanakiri, Cambodia.**

Kerkhof K<sup>1,2</sup>, Sluydts V<sup>3,4</sup>, Heng S<sup>5</sup>, Kim S<sup>6</sup>, Pareyn M<sup>3,7</sup>, Willen L<sup>3</sup>, Canier L<sup>6</sup>, Sovannaroeth S<sup>5</sup>, Ménard D<sup>6</sup>, Sochantha T<sup>5</sup>, Coosemans M<sup>3,7</sup>, Durnez L<sup>3</sup>.

**BACKGROUND:**

Malaria transmission is highly heterogeneous, especially in low endemic countries, such as Cambodia. This results in geographical clusters of residual transmission in the dry, low transmission season, which can fuel the transmission to wider areas or populations during the wet season. A better understanding of spatial clustering of malaria can lead to a more efficient, targeted strategy to reduce malaria transmission. This study aims to evaluate the potential of the use of serological markers to define spatial patterns in malaria exposure.

**METHODS:**

Blood samples collected in a community-based randomized trial performed in 98 high endemic communities in Ratanakiri province, north-eastern Cambodia, were screened with a multiplex serological assay for five serological markers (three *Plasmodium falciparum* and two *Plasmodium vivax*). The antibody half-lives range from approximately six months until more than two years. Geographical heterogeneity in malaria transmission was examined using a spatial scan statistic on serology, PCR prevalence and malaria incidence rate data. Furthermore, to identify behavioural patterns or intrinsic factors associated with malaria exposure (antibody levels), risk factor analyses were performed by using multivariable random effect logistic regression models. The serological outcomes were then compared to PCR prevalence and malaria incidence data.

**RESULTS:**

**A total of 6502 samples from two surveys were screened in an area where the average parasite prevalence estimated by PCR among the selected villages is 3.4 %. High-risk malaria pockets were observed adjacent to the 'Tonle San River' and neighbouring Vietnam for all three sets of data (serology, PCR prevalence and malaria incidence rates). The main risk factors for all *P. falciparum* antigens and *P. vivax* MSP1.19 are age, ethnicity and staying overnight at the plot hut.**

**CONCLUSION:**

It is possible to identify similar malaria pockets of higher malaria transmission together with the potential risk factors by using serology instead of PCR prevalence or malaria incidence data. **In north-eastern Cambodia, the serological markers show that malaria transmission occurs mainly in adults staying overnight in plot huts in the field.** Pf.GLURP.R2 showed a shrinking pocket of malaria transmission over time, and Pf.MSP1.19, CSP, PvAMA1 were also informative for current infection to a lesser extent. Therefore, serology could contribute in future research. However, further in-depth research in selecting the best combination of antigens is required.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5069850/>

J Infect Dis. 2016 Jul 15;214(2):329-38. doi: 10.1093/infdis/jiw147. Epub 2016 Apr 10.

**Effective Antimalarial Chemoprevention in Childhood Enhances the Quality of CD4+ T Cells and Limits Their Production of Immunoregulatory Interleukin 10.**

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**BACKGROUND:**



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Experimental inoculation of viable *Plasmodium falciparum* sporozoites administered with chemoprevention targeting blood-stage parasites results in protective immunity. It is unclear whether chemoprevention similarly enhances immunity following natural exposure to malaria.

### METHODS:

We assessed *P. falciparum*-specific T-cell responses among Ugandan children who were randomly assigned to receive monthly dihydroartemisinin-piperaquine (DP; n = 87) or no chemoprevention (n = 90) from 6 to 24 months of age, with pharmacologic assessments for adherence, and then clinically followed for an additional year.

### RESULTS:

During the intervention, monthly DP reduced malaria episodes by 55% overall ( $P < .001$ ) and by 97% among children who were highly adherent to DP ( $P < .001$ ). In the year after the cessation of chemoprevention, children who were highly adherent to DP had a 55% reduction in malaria incidence as compared to children given no chemoprevention ( $P = .004$ ). Children randomly assigned to receive DP had higher frequencies of blood-stage specific CD4(+) T cells coproducing interleukin-2 and tumor necrosis factor  $\alpha$  ( $P = .003$ ), which were associated with protection from subsequent clinical malaria and parasitemia, and fewer blood-stage specific CD4(+) T cells coproducing interleukin-10 and interferon  $\gamma$  ( $P = .001$ ), which were associated with increased risk of malaria.

### CONCLUSIONS:

In this setting, effective antimalarial chemoprevention fostered the development of CD4(+) T cells that coproduced interleukin 2 and tumor necrosis factor  $\alpha$  and were associated with prospective protection, while limiting CD4(+) T-cell production of the immunoregulatory cytokine IL-10.

Free access: <https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jiw147>

## Treatment of uncomplicated malaria

[Malar J.](#) 2016 Sep 6;15:455. doi: 10.1186/s12936-016-1444-x.

**[In vivo efficacy of artesunate-amodiaquine and artemether-lumefantrine for the treatment of uncomplicated falciparum malaria: an open-randomized, non-inferiority clinical trial in South Kivu, Democratic Republic of Congo.](#)**

[de Wit M](#)<sup>1</sup>, [Funk AL](#)<sup>2</sup>, [Moussally K](#)<sup>2</sup>, [Nkuba DA](#)<sup>2</sup>, [Siddiqui R](#)<sup>3</sup>, [Bil K](#)<sup>2</sup>, [Piriou E](#)<sup>2</sup>, [Bart A](#)<sup>4</sup>, [Bahizi Bizoza P](#)<sup>5</sup>, [Bousema T](#)<sup>6,7</sup>.

### BACKGROUND:

Between 2009 and 2012, malaria cases diagnosed in a Médecins sans Frontières programme have increased fivefold in Baraka, South Kivu, Democratic Republic of the Congo (DRC). The cause of this increase is not known. An in vivo drug efficacy trial was conducted to determine whether increased treatment failure rates may have contributed to the apparent increase in malaria diagnoses.

### METHODS:

In an open-randomized non-inferiority trial, the efficacy of artesunate-amodiaquine (ASAQ) was compared to artemether-lumefantrine (AL) for the treatment of uncomplicated falciparum malaria in 288 children aged 6-59 months. Included children had directly supervised treatment and were then followed for 42 days with weekly clinical and parasitological evaluations. The blood samples of children found to have recurring parasitaemia within 42 days were checked by PCR to confirm whether or not this was due to reinfection or recrudescence (i.e. treatment failure).

### RESULTS:

Out of 873 children screened, 585 (67 %) were excluded and **288 children were randomized to either ASAQ or AL. At day 42 of follow up, the treatment efficacy of ASAQ was 78 % before and 95 % after PCR correction for re-infections. In the AL-arm, treatment efficacy was 84 % before and 99.0 % after PCR correction.** Treatment efficacy after PCR correction was within the margin of non-inferiority as set for this study. Fewer children in the AL arm reported adverse reactions.

### CONCLUSIONS:

ASAQ is still effective as a treatment for uncomplicated malaria in Baraka, South Kivu, DRC. In this region, AL may have higher efficacy but additional trials are required to draw this conclusion with confidence. The high re-infection rate in South-Kivu indicates intense malaria transmission. Trial registration [NCT02741024](https://www.clinicaltrials.gov/ct2/show/study?term=NCT02741024).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013565/>

[Lancet Infect Dis](#). 2016 Oct;16(10):1123-33. doi: 10.1016/S1473-3099(16)30020-2. Epub 2016 Jul 16.

**Comparison of artesunate-mefloquine and artemether-lumefantrine fixed-dose combinations for treatment of uncomplicated Plasmodium falciparum malaria in children younger than 5 years in sub-Saharan Africa: a randomised, multicentre, phase 4 trial.**  
[Sirima SB](#)<sup>1</sup>, [Ogutu B](#)<sup>2</sup>, [Lusingu JP](#)<sup>3</sup>, [Mtoro A](#)<sup>4</sup>, [Mrango Z](#)<sup>5</sup>, [Ouedraogo A](#)<sup>1</sup>, [Yaro JB](#)<sup>1</sup>, [Onyango KO](#)<sup>2</sup>, [Gesase S](#)<sup>3</sup>, [Mnkande E](#)<sup>4</sup>, [Ngocho JS](#)<sup>5</sup>, [Ackermann I](#)<sup>6</sup>, [Aubin F](#)<sup>6</sup>, [Vanraes J](#)<sup>7</sup>, [Strub N](#)<sup>7</sup>, [Carn G](#)<sup>8</sup>.

### BACKGROUND:

WHO recommends combinations of an artemisinin derivative plus an antimalarial drug of longer half-life as treatment options for uncomplicated Plasmodium falciparum infection. In Africa, artemether-lumefantrine is the most widely used artemisinin-based combination therapy, whereas artesunate-mefloquine is used infrequently because of a perceived poor tolerance to mefloquine. WHO recommends reconsideration of the use of artesunate-mefloquine in Africa.

**We compared the efficacy and safety of fixed-dose artesunate-mefloquine with that of artemether-lumefantrine for treatment of children younger than 5 years with uncomplicated P falciparum malaria.**

### METHODS:

We did this multicentre, phase 4, open-label, non-inferiority trial in Burkina Faso, Kenya, and Tanzania. Children aged 6-59 months with uncomplicated malaria were randomly assigned (1:1), via a computer-generated randomisation list, to receive 3 days' treatment with either one or two artesunate-mefloquine tablets (25 mg artesunate and 55 mg mefloquine) once a day or one or two artemether-lumefantrine tablets (20 mg artemether and 120 mg lumefantrine) twice a day. Parasitological assessments were done independently by two microscopists who were blinded to treatment allocation. The primary outcome was the PCR-corrected rate of adequate clinical and parasitological response (ACPR) at day 63 in the per-protocol population. Non-inferiority was shown if the lower limit of the 95% CI for the difference between groups was greater than -5%. Early vomiting was monitored and neuropsychiatric status assessed regularly during follow-up. This study is registered with ISRCTN, number ISRCTN17472707, and the Pan African Clinical Trials Registry, number PACTR201202000278282.

### FINDINGS:

945 children were enrolled and randomised, **473 to artesunate-mefloquine and 472 to artemether-lumefantrine.** The per-protocol population consisted of 407 children in each group. **The PCR-corrected ACPR rate at day 63 was 90.9% (370 patients) in the artesunate-mefloquine group and 89.7% (365 patients) in the artemether-lumefantrine group**

(treatment difference 1·23%, 95% CI -2·84% to 5·29%). At 72 h after the start of treatment, no child had detectable parasitaemia and less than 6% had fever, with a similar number in each group (21 in the artesunate-mefloquine group vs 24 in the artemether-lumefantrine group). The safety profiles of artesunate-mefloquine and artemether-lumefantrine were similar, with low rates of early vomiting (71 [15·3%] of 463 patients in the artesunate-mefloquine group vs 79 [16·8%] of 471 patients in the artemether-lumefantrine group in any of the three dosing days), few neurological adverse events (ten [2·1%] of 468 vs five [1·1%] of 465), and no detectable psychiatric adverse events.

### INTERPRETATION:

Artesunate-mefloquine is effective and safe, and an important treatment option, for children younger than 5 years with uncomplicated *P falciparum* malaria in Africa.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5030279/>

Malar J. 2016 Aug 26;15(1):435. doi: 10.1186/s12936-016-1430-3.

### Adding a single low-dose of primaquine (0.25 mg/kg) to artemether-lumefantrine did not compromise treatment outcome of uncomplicated *Plasmodium falciparum* malaria in Tanzania: a randomized, single-blinded clinical trial.

Mwaiswelo R<sup>1</sup>, Ngasala B<sup>2</sup>, Jovel I<sup>3</sup>, Aydin-Schmidt B<sup>3</sup>, Gosling R<sup>4,5</sup>, Premji Z<sup>6</sup>, Mmbando B<sup>7</sup>, Björkman A<sup>3</sup>, Mårtensson A<sup>8</sup>.

### BACKGROUND:

The World Health Organization (WHO) recently recommended the **addition of a single low-dose of the gametocytocidal drug primaquine (PQ) to artemisinin-based combination therapy (ACT)** in low transmission settings as a component of pre-elimination or elimination programmes. However, it is unclear whether that influences the ACT cure rate. **The study assessed treatment outcome of artemether-lumefantrine (AL) plus a single PQ dose (0.25 mg/kg) versus standard AL regimen for treatment of acute uncomplicated *Plasmodium falciparum* malaria in Tanzania.**

### METHODS:

A randomized, single-blinded, clinical trial was conducted in Yombo, Bagamoyo district, Tanzania. Acute uncomplicated *P. falciparum* malaria patients aged  $\geq 1$  year, with the exception of pregnant and lactating women, were enrolled and treated with AL plus a single PQ dose (0.25 mg/kg) or AL alone under supervision. PQ was administered together with the first AL dose. Clinical and laboratory assessments were performed at 0, 8, 24, 36, 48, 60, and 72 h and on days 7, 14, 21, and 28. The primary end-point was a polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response (ACPR) on day 28. Secondary outcomes included: fever and asexual parasitaemia clearance, proportion of patients with PCR-determined parasitaemia on day 3, and proportion of patients with *Pfmdr1* N86Y and *Pfprt* K76T on days 0, 3 and day of recurrent infection.

### RESULTS:

Overall 220 patients were enrolled, 110 were allocated AL + PQ and AL, respectively. Parasite clearance by microscopy was fast, but PCR detectable parasitaemia on day 3 was 31/109 (28.4 %) and 29/108 (26.9 %) in patients treated with AL + PQ and AL, respectively ( $p = 0.79$ ). Day 28 PCR-adjusted ACPR and re-infection rate was 105/105 (100 %) and 101/102 (99 %) ( $p = 0.31$ ), and 5/107 (4.7 %) and 5/8 (4.8 %) ( $p = 0.95$ ), in AL + PQ and AL arm, respectively. There was neither any statistically significant difference in the proportion of *Pfmdr1* N86Y or *Pfprt* K76T between treatment arms on days 0, 3 and day of recurrent infection, nor within treatment arms between days 0 and 3 or day 0 and day of recurrent infection.

### CONCLUSION:

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The new WHO recommendation of adding a single low-dose of PQ to AL did not compromise treatment outcome of uncomplicated *P. falciparum* malaria in Tanzania. Trial registration number [NCT02090036](https://www.clinicaltrials.gov/ct2/show/study?term=NCT02090036).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5002101/>

[Acta Trop.](#) 2016 Aug;160:1-8. doi: 10.1016/j.actatropica.2016.04.002. Epub 2016 Apr 4.

### **Risk factors for *Plasmodium falciparum* and *Plasmodium vivax* gametocyte carriage in Papua New Guinean children with uncomplicated malaria.**

[Karl S](#)<sup>1</sup>, [Laman M](#)<sup>2</sup>, [Moore BR](#)<sup>3</sup>, [Benjamin JM](#)<sup>2</sup>, [Salib M](#)<sup>2</sup>, [Lorry L](#)<sup>2</sup>, [Maripal S](#)<sup>2</sup>, [Siba P](#)<sup>2</sup>, [Robinson LJ](#)<sup>4</sup>, [Mueller I](#)<sup>1</sup>, [Davis TM](#)<sup>5</sup>.

#### **Abstract**

There are limited data on gametocytaemia risk factors before/after treatment with artemisinin combination therapy in children from areas with transmission of multiple *Plasmodium* species. **We utilised data from a randomised trial comparing artemether-lumefantrine (AL) and artemisinin-naphthoquine (AN) in 230 Papua New Guinean children aged 0.5-5 years with uncomplicated malaria in whom determinants of gametocytaemia by light microscopy were assessed at baseline** using logistic regression and during follow-up using multilevel mixed effects modelling. Seventy-four (32%) and 18 (8%) children presented with *P. falciparum* and *P. vivax* gametocytaemia, respectively. Baseline *P. falciparum* gametocytaemia was associated with Hackett spleen grade 1 (odds ratio (95% CI) 4.01 (1.60-10.05) vs grade 0;  $P<0.001$ ) and haemoglobin (0.95 (0.92-0.97) per 1g/L increase;  $P<0.001$ ), and *P. falciparum* asexual parasitaemia in slide-positive cases (0.36 (0.19-0.68) for a 10-fold increase;  $P=0.002$ ). Baseline *P. vivax* gametocytaemia was associated with Hackett grade 2 (12.66 (1.31-122.56);  $P=0.028$ ), mixed *P. falciparum/vivax* infection (0.16 (0.03-1.00);  $P=0.050$ ), *P. vivax* asexual parasitaemia (5.68 (0.98-33.04);  $P=0.053$ ) and haemoglobin (0.94 (0.88-1.00);  $P=0.056$ ). For post-treatment *P. falciparum* gametocytaemia, independent predictors were AN vs AL treatment (4.09 (1.43-11.65)), haemoglobin (0.95 (0.93-0.97)), presence/absence of *P. falciparum* asexual forms (3.40 (1.66-6.80)) and day post-treatment (0.086 (0.02-0.90)) ( $P<0.001$ ). Post-treatment *P. vivax* gametocytaemia was predicted by presence of *P. vivax* asexual forms (596 (12-28,433);  $P<0.001$ ). **Consistent with slow *P. falciparum* gametocyte maturation, low haemoglobin, low asexual parasite density and higher spleen grading, markers of increased prior infection exposure/immunity, were strong associates of pre-treatment gametocyte positivity. The persistent inverse association between *P. falciparum* gametocytaemia and haemoglobin during follow-up suggests an important role for bone marrow modulation of gametocytogenesis.** In *P. vivax* infections, baseline and post-treatment gametocyte carriage was positively related to the acute parasite burden, reflecting the close association between the development of asexual and sexual forms.

[Malar J.](#) 2017 May 23;16(1):215. doi: 10.1186/s12936-017-1858-0.

### **Safety and tolerability of adjunctive rosiglitazone treatment for children with uncomplicated malaria.**

[Varo R](#)<sup>1,2</sup>, [Crowley VM](#)<sup>3</sup>, [Sitoe A](#)<sup>2</sup>, [Madrid L](#)<sup>1,2</sup>, [Serghides I](#)<sup>4,5,6</sup>, [Bila R](#)<sup>2</sup>, [Mucavele H](#)<sup>2</sup>, [Mayor A](#)<sup>1,2</sup>, [Bassat Q](#)<sup>7,8,9</sup>, [Kain KC](#)<sup>3,10,11</sup>.

#### **BACKGROUND:**

Despite the widespread use and availability of rapidly acting anti-malarials, the fatality rate of severe malaria in sub-Saharan Africa remains high. Adjunctive therapies that target the host

response to malaria infection may further decrease mortality over that of anti-malarial agents alone. **Peroxisome proliferator-activated receptor-gamma agonists (e.g. rosiglitazone) have been shown to act on several pathways implicated in the pathogenesis of severe malaria** and may improve clinical outcome as an adjunctive intervention.

### **METHODS:**

In this study, the **safety and tolerability of adjunctive rosiglitazone in paediatric uncomplicated malaria infection was evaluated in Mozambique**, as a prelude to its evaluation in a randomized controlled trial in paediatric severe malaria. The study was a prospective, randomized, double-blind, placebo-controlled, phase IIa trial of rosiglitazone (0.045 mg/kg/dose) twice daily for 4 days versus placebo as adjunctive treatment in addition to Mozambican standard of care (artemisinin combination therapy Coartem<sup>®</sup>) in children with uncomplicated malaria. The primary outcomes were tolerability and safety, including clinical, haematological, biochemical, and electrocardiographic evaluations.

### **RESULTS:**

Thirty children were enrolled: 20 were assigned to rosiglitazone and 10 to placebo. Rosiglitazone treatment did not induce hypoglycaemia nor significantly alter clinical, biochemical, haematological, or electrocardiographic parameters.

### **CONCLUSIONS:**

Adjunctive rosiglitazone was safe and well-tolerated in children with uncomplicated malaria, permitting the extension of its evaluation as adjunctive therapy for severe malaria. The trial is registered with Clinicaltrials.gov, [NCT02694874](https://www.clinicaltrials.gov/ct2/show/study?term=NCT02694874).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5442675/>

## Treatment of severe or complicated malaria

[Paediatr Int Child Health](#). 2017 May;37(2):139-143. doi: 10.1080/20469047.2016.1209883. Epub 2016 Jul 26.

### **Effect of quinine and artesunate combination therapy on platelet count of children with severe malaria.**

[Gupta P](#)<sup>1</sup>, [Narang M](#)<sup>1</sup>, [Gomber S](#)<sup>1</sup>, [Saha R](#)<sup>2</sup>.

#### **Abstract**

#### **BACKGROUND:**

There are several case reports of quinine-induced thrombocytopenia but no clinical trials to ascertain its incidence and significance in severe malaria.

#### **OBJECTIVES:**

The primary objective was to **assess the effect of quinine on the platelet count in children with severe malaria** and to compare it with artesunate combination therapy (ACT), and the secondary objective was to assess outcome of treatment with quinine and ACT.

#### **METHODS:**

An open-labelled, randomised, controlled trial was undertaken in 100 children aged 6 months to 12 years who were diagnosed with malaria by microscopy and/or rapid diagnostic test kits with at least one WHO clinical or laboratory criterion for severe malaria. All subjects were commenced on either quinine or ACT. Clindamycin was added to artesunate as a combination drug (ACT). It was also given to patients on quinine to avoid its confounding effect on the results. **Platelet counts were undertaken every 24 hours for 7 consecutive days**, temperature and coma score (Blantyre coma score  $\geq 3$  in children  $< 4$  years or Glasgow coma score  $\geq 13$  in children  $> 4$  years) was recorded 6-hourly and peripheral smears were taken 12-hourly until two



consecutively negative smears were obtained. The primary outcome was a fall in the platelet count by  $\geq 20\%$  from the time of drug initiation until day 7. The secondary outcome was comparison of the efficacy, parasite clearance time, fever clearance time, coma recovery time and adverse effects of quinine vs ACT.

### RESULTS:

**30.4% patients in the quinine group (n = 48) had  $\geq 20\%$  fall in platelet count and 10.8% of patients in the ACT group (n = 46) (P = 0.02).** Despite the fall in platelet count, there was no bleeding. The efficacy of ACT was significantly better than quinine but the other treatment outcomes showed insignificant difference.

### CONCLUSION:

Quinine should be used with caution in patients with severe malaria because of the potential risk of quinine-induced thrombocytopenia.

[Malar J. 2016 Dec 7;15\(1\):587.](#)

### Economic evaluation of artesunate and three quinine regimens in the treatment of severe malaria in children at the Ebolowa Regional Hospital-Cameroon: a cost analysis.

[Maka DE<sup>1</sup>](#), [Chiabi A<sup>2,3</sup>](#), [Obadeyi B<sup>4</sup>](#), [Mah E<sup>2,3</sup>](#), [Nguefack S<sup>2,3</sup>](#), [Nana P<sup>5</sup>](#), [Mbacham W<sup>6</sup>](#), [Mbonda E<sup>2,3</sup>](#).

### BACKGROUND:

Severe malaria is a leading cause of morbidity and mortality in under-fives in sub-Saharan Africa. Recently quinine has been replaced by artesunate as the first-line drug in the treatment of severe malaria in Cameroon. Artesunate has been shown to be cost-effective in African children, but whether these findings are transferable to Cameroonian children remains to be explored.

### OBJECTIVES:

To conduct a cost-analysis of four different regimens used in the treatment from the perspective of the healthcare payer.

### METHODS:

An economic evaluation alongside a randomized comparative study was conducted in children aged 3 months to 15 years, admitted at the Ebolowa Regional Hospital with severe malaria due to *Plasmodium falciparum*. **Patients were randomized to receive one of the four treatment alternatives. Group 1 (ARTES) received parenteral artesunate at 2.4 mg/kg at H<sub>0</sub>, H<sub>12</sub>, H<sub>24</sub> and then once daily; Group 2 (QLD) received a loading dose of quinine base at 16.6 mg/kg followed 8 h later by an 8-hourly maintenance dose of 8.3 mg/kg quinine base; Group 3 (QNLD3) received 8.3 mg/kg quinine base every 8 h, and Group 4 (QNLD2) received 12.5 mg/kg quinine base every 12 h.** The main outcome measure for effectiveness of treatment was the parasite reduction rate. Based on a healthcare perspective, an evaluation of direct medical costs was done, including costs of anti-malarials, nursing care materials, adjuvant treatment, laboratory investigations, hospitalisation and professional fees. Guided by a cost minimalization approach, the relative costs of these treatment alternatives was compared and reported.

### RESULTS:

**Overall cost was higher for ARTES group at \$65.14 (95% CI \$57.68-72.60) than for quinine groups (\$52.49-\$62.40), but the difference was not statistically significant.** Cost of the anti-malarial drug was significantly higher for artesunate-treated patients than for quinine-treated patients, whereas cost of hospitalization was significantly lower for artesunate-treated patients than for quinine-treated patients. Incremental analysis of ARTES against QLD as a baseline resulted in an ICER of \$46.8/PRR<sub>24</sub> and suggests ARTES as the most cost effective of all four treatment options.



## CONCLUSION:

Artesunate is a cost effective malaria treatment option relative to quinine alternatives with the lowest incremental cost per unit of effectiveness.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142138/>

## Treatment of vivax malaria

*PLoS Med.* 2017 May 16;14(5):e1002299. doi: 10.1371/journal.pmed.1002299. eCollection 2017 May.

### Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of Plasmodium vivax infection in Ethiopia: A randomized controlled trial.

[Abreha T](#)<sup>1</sup>, [Hwang J](#)<sup>2,3</sup>, [Thriemer K](#)<sup>4</sup>, [Tadesse Y](#)<sup>1</sup>, [Girma S](#)<sup>1</sup>, [Melaku Z](#)<sup>1</sup>, [Assef A](#)<sup>5</sup>, [Kassa M](#)<sup>5</sup>, [Chatfield MD](#)<sup>4</sup>, [Landman KZ](#)<sup>6</sup>, [Chenet SM](#)<sup>6</sup>, [Lucchi NW](#)<sup>6</sup>, [Udhayakumar V](#)<sup>6</sup>, [Zhou Z](#)<sup>6</sup>, [Shi YP](#)<sup>6</sup>, [Kachur SP](#)<sup>6</sup>, [Jima D](#)<sup>5</sup>, [Kebede A](#)<sup>5</sup>, [Solomon H](#)<sup>7</sup>, [Mekasha A](#)<sup>8</sup>, [Alemayehu BH](#)<sup>1</sup>, [Malone JL](#)<sup>2</sup>, [Dissanayake G](#)<sup>9</sup>, [Teka H](#)<sup>9</sup>, [Auburn S](#)<sup>4</sup>, [von Seidlein L](#)<sup>10</sup>, [Price RN](#)<sup>4,11</sup>.

## BACKGROUND:

Recent efforts in malaria control have resulted in great gains in reducing the burden of *Plasmodium falciparum*, but *P. vivax* has been more refractory. Its ability to form dormant liver stages confounds control and elimination efforts. **To compare the efficacy and safety of primaquine regimens for radical cure**, we undertook a randomized controlled trial in Ethiopia.

## METHODS AND FINDINGS:

**Patients with normal glucose-6-phosphate dehydrogenase status with symptomatic *P. vivax* mono-infection were enrolled and randomly assigned to receive either chloroquine (CQ) or artemether-lumefantrine (AL), alone or in combination with 14 d of semi-supervised primaquine (PQ) (3.5 mg/kg total).** A total of 398 patients (n = 104 in the CQ arm, n = 100 in the AL arm, n = 102 in the CQ+PQ arm, and n = 92 in the AL+PQ arm) were followed for 1 y, and recurrent episodes were treated with the same treatment allocated at enrolment. The primary endpoints were the risk of *P. vivax* recurrence at day 28 and at day 42. **The risk of recurrent *P. vivax* infection at day 28 was 4.0% (95% CI 1.5%-10.4%) after CQ treatment and 0% (95% CI 0%-4.0%) after CQ+PQ. The corresponding risks were 12.0% (95% CI 6.8%-20.6%) following AL alone and 2.3% (95% CI 0.6%-9.0%) following AL+PQ.** On day 42, the risk was 18.7% (95% CI 12.2%-28.0%) after CQ, 1.2% (95% CI 0.2%-8.0%) after CQ+PQ, 29.9% (95% CI 21.6%-40.5%) after AL, and 5.9% (95% CI 2.4%-13.5%) after AL+PQ (overall p < 0.001). In those not prescribed PQ, the risk of recurrence by day 42 appeared greater following AL treatment than CQ treatment (HR = 1.8 [95% CI 1.0-3.2]; p = 0.059). At the end of follow-up, the incidence rate of *P. vivax* was 2.2 episodes/person-year for patients treated with CQ compared to 0.4 for patients treated with CQ+PQ (rate ratio: 5.1 [95% CI 2.9-9.1]; p < 0.001) and 2.3 episodes/person-year for AL compared to 0.5 for AL+PQ (rate ratio: 6.4 [95% CI 3.6-11.3]; p < 0.001). There was no difference in the occurrence of adverse events between treatment arms. The main limitations of the study were the early termination of the trial and the omission of haemoglobin measurement after day 42, resulting in an inability to estimate the cumulative risk of anaemia.

## CONCLUSIONS:

**Despite evidence of CQ-resistant *P. vivax*, the risk of recurrence in this study was greater following treatment with AL unless it was combined with a supervised course of PQ. PQ**

combined with either CQ or AL was well tolerated and reduced recurrence of vivax malaria by 5-fold at 1 y.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5433686/>

## **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)

## **Maternal health**

(see also Malaria)

[BMC Pregnancy Childbirth](#). 2017 May 8;17(1):137. doi: 10.1186/s12884-017-1313-9.

[Intravenous iron sucrose v/s oral ferrous fumarate for treatment of anemia in pregnancy. A randomized controlled trial.](#)

[Bhavi SB](#)<sup>1</sup>, [Jaju PB](#)<sup>2</sup>.

### **Abstract**

#### **BACKGROUND:**

The objective of this study was to compare the efficacy, safety and tolerability of intravenous iron sucrose with that of oral ferrous fumarate in iron deficiency anemia during 14 to 34 weeks of pregnancy.

#### **METHODS:**

A randomized controlled trial was performed involving 112 patients attending the antenatal clinic at Shri B.M.Patil Medical college Hospital, Bijapur from October 2011 to August 2012, with hemoglobin levels between 70-110 g/L and serum ferritin of < 15 ng/ml. **In the intravenous group, 200 mg of iron sucrose was administered in 100 ml 0.9% sodium chloride per day. Participants in the oral group were given 200 mg of ferrous fumarate per day.** The primary outcome measures for the trial, haemoglobin and serum ferritin levels were measured after 4 weeks. Statistical significance was assessed using Student's t-test.

#### **RESULTS:**

**The change in haemoglobin in women receiving intravenous iron was higher than with oral ferrous fumarate  $22 \pm 11.5$  g/L vs  $12 \pm 9$  g/L ( $p < 0.0001$ ). Similarly the change of serum ferritin was significantly higher in women receiving intravenous iron compared to oral iron. 55% participants in the intravenous group had an improvement in haemoglobin more than 20 g/L compared to only 11% of the oral therapy group. 48% of patients in I.V group showed increase in ferritin level between 51 to 100 ng/ml in comparison to only 3.5% in oral group. Intravenous iron sucrose is an effective in correction of anemia in pregnancy or iron store depletion.**

#### **CONCLUSION:**

Intravenous iron sucrose is more effective than 200 mg a day ferrous fumarate in increasing maternal iron stores.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5422878/>

### Comment

*The IV iron sucrose was given as no more than 200mg per day, to a total dose which depended on what the starting Hb was. Based on the calculation in the paper (listed below), typically this would take 3 days to give the full dose, so the intervention required hospitalisation for this time. Total dose required = weight in kg × (target Hb in g/L – Actual Hb in g/L) × 0.24 + 500 mg rounded up to the nearest multiple of 100 mg*

[BMC Public Health](#). 2016 Oct 17;16(1):1087.

### Does mode of follow-up influence contraceptive use after medical abortion in a low-resource setting? Secondary outcome analysis of a non-inferiority randomized controlled trial.

[Paul M](#)<sup>1</sup>, [Iyengar SD](#)<sup>2</sup>, [Essén B](#)<sup>3</sup>, [Gemzell-Danielsson K](#)<sup>4</sup>, [Iyengar K](#)<sup>2,4</sup>, [Bring J](#)<sup>5</sup>, [Klingberg-Allvin M](#)<sup>5,6</sup>.

#### **BACKGROUND:**

Post-abortion contraceptive use in India is low and the use of modern methods of contraception is rare, especially in rural areas. This study primarily compares contraceptive use among women whose abortion outcome was assessed in-clinic with women who assessed their abortion outcome at home, in a low-resource, primary health care setting. Moreover, it investigates how background characteristics and abortion service provision influences contraceptive use post-abortion.

#### **METHODS:**

A randomized controlled, non-inferiority, trial (RCT) compared clinic follow-up with home-assessment of abortion outcome at 2 weeks post-abortion. Additionally, contraceptive-use at 3 months post-abortion was investigated through a cross-sectional follow-up interview with a largely urban sub-sample of women from the RCT. **Women seeking abortion with a gestational age of up to 9 weeks and who agreed to a 2-week follow-up were included (n = 731).** Women with known contraindications to medical abortions, Hb < 85 mg/l and aged below 18 were excluded. Data were collected between April 2013 and August 2014 in six primary health-care clinics in Rajasthan. A computerised random number generator created the randomisation sequence (1:1) in blocks of six. Contraceptive use was measured at 2 weeks among women successfully followed-up (n = 623) and 3 months in the sub-set of women who were included if they were recruited at one of the urban study sites, owned a phone and agreed to a 3-month follow-up (n = 114).

#### **RESULTS:**

**There were no differences between contraceptive use and continuation between study groups at 3 months (76 % clinic follow-up, 77 % home-assessment),** however women in the clinic follow-up group were most likely to adopt a contraceptive method at 2 weeks ( $62 \pm 12$  %), while women in the home-assessment group were most likely to adopt a method after next menstruation ( $60 \pm 13$  %). Fifty-two per cent of women who initiated a method at 2 weeks chose the 3-month injection or the copper intrauterine device. Only 4 % of women preferred sterilization. Caste, educational attainment, or type of residence did not influence contraceptive use.

#### **CONCLUSIONS:**

Simplified follow-up after early medical abortion will not change women's opportunities to access contraception in a low-resource setting, if contraceptive services are provided as intra-abortion services as early as on day one. Women's postabortion contraceptive use at 3 months is unlikely to be affected by mode of followup after medical abortion, also in a low-resource

setting. Clinical guidelines need to encourage intra-abortion contraception, offering the full spectrum of evidence-based methods, especially long-acting reversible methods.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5066281/>

[Lancet](#). 2016 Jul 2;388(10039):62-72. doi: 10.1016/S0140-6736(16)00204-X. Epub 2016 May 4.

### Caesarean section surgical techniques: 3 year follow-up of the CORONIS fractional, factorial, unmasked, randomised controlled trial.

[CORONIS collaborative group](#), [Abalos E](#), [Addo V](#), [Brocklehurst P](#), [El Sheikh M](#), [Farrell B](#), [Gray S](#), [Hardy P](#), [Juszczak E](#), [Mathews JE](#), [Naz Masood S](#), [Oyarzun E](#), [Oyieke J](#), [Sharma JB](#), [Spark P](#).

#### **BACKGROUND:**

The CORONIS trial reported differences in short-term maternal morbidity when comparing five pairs of alternative surgical techniques for caesarean section. Here we report outcomes at 3 years follow-up.

#### **METHODS:**

The CORONIS trial was a pragmatic international  $2 \times 2 \times 2 \times 2$  non-regular fractional, factorial, unmasked, randomised controlled trial done at 19 sites in Argentina, Chile, Ghana, India, Kenya, Pakistan, and Sudan. Pregnant women were eligible if they were to undergo their first or second caesarean section through a planned transverse abdominal incision. Women were randomly assigned by a secure web-based allocation system to one intervention from each of the three assigned pairs. All investigators, surgeons, and participants were unmasked to treatment allocation. In this follow-up study, **we compared outcomes at 3 years following blunt versus sharp abdominal entry, exteriorisation of the uterus for repair versus intra-abdominal repair, single versus double layer closure of the uterus, closure versus non-closure of the peritoneum, and chromic catgut versus polyglactin-910 for uterine repair.** Outcomes included pelvic pain; deep dyspareunia; hysterectomy and outcomes of subsequent pregnancies. Outcomes were assessed masked to the original trial allocation. This trial is registered with the Current Controlled Trials registry, number ISRCTN31089967.

#### **FINDINGS:**

Between Sept 1, 2011, and Sept 30, 2014, 13,153 (84%) women were followed-up for a mean duration of 3·8 years (SD 0·86). For blunt versus sharp abdominal entry there was no evidence of a difference in risk of abdominal hernias (adjusted RR 0·66; 95% CI 0·39-1·11). **We also recorded no evidence of a difference in risk of death or serious morbidity of the children born at the time of trial entry (0·99, 0·83-1·17).** For exteriorisation of the uterus versus intra-abdominal repair there was no evidence of a difference in risk of infertility (0·91, 0·71-1·18) or of ectopic pregnancy (0·50, 0·15-1·66). For single versus double layer closure of the uterus there was no evidence of a difference in maternal death (0·78, 0·46-1·32) or a composite of pregnancy complications (1·20, 0·75-1·90). For closure versus non-closure of the peritoneum there was no evidence of a difference in any outcomes relating to symptoms associated with pelvic adhesions such as infertility (0·80, 0·61-1·06). For chromic catgut versus polyglactin-910 sutures there was no evidence of a difference in the main comparisons for adverse pregnancy outcomes in a subsequent pregnancy, such as uterine rupture (3·05, 0·32-29·29). Overall, severe adverse outcomes were uncommon in these settings.

#### **INTERPRETATION:**

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Although our study was not powered to detect modest differences in rare but serious events, there was no evidence to favour one technique over another. Other considerations will probably affect clinical practice, such as the time and cost saving of different approaches.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4930950/>

## Maternal nutrition and micronutrient supplementation

[Am J Clin Nutr.](#) 2016 Oct;104(4):1175-1182. Epub 2016 Sep 7.

### **Effects of prenatal multiple micronutrient supplementation on growth and cognition through 2 y of age in rural Bangladesh: the JiVitA-3 Trial.**

[Christian P](#)<sup>1</sup>, [Kim J](#)<sup>2</sup>, [Mehra S](#)<sup>3</sup>, [Shaikh S](#)<sup>4</sup>, [Ali H](#)<sup>4</sup>, [Shamim AA](#)<sup>5</sup>, [Wu L](#)<sup>3</sup>, [Klemm R](#)<sup>3</sup>, [Labrique AB](#)<sup>3</sup>, [West KP Jr](#)<sup>3</sup>.

#### **BACKGROUND:**

Childhood undernutrition may have prenatal origins, and the impact of prenatal interventions on postnatal growth is not well known.

#### **OBJECTIVE:**

We assessed the effects of prenatal multiple micronutrient (MM) supplementation on child growth and cognitive development.

#### **DESIGN:**

In a cluster-randomized controlled trial in rural Bangladesh, **prenatal MM supplementation compared with iron-folic acid (IFA) supplementation was examined for its impact on growth assessed longitudinally from birth up to 24 mo of age (n = 8529) and, in a subsample (n = 734), on cognitive function at 24 mo of age by use of the Bayley scales of infant and toddler development-third edition test.**

#### **RESULTS:**

Prevalence of stunting at birth [length for age z score (LAZ): <-2] was 31.9% in the MM and 35.7% in the IFA groups (P < 0.001); however, LAZ increased during the first 3-4 mo in both groups. With the use of a linear random-effects model, prenatal MM-exposed children sustained a higher mean predicted LAZ of ~ 0.10 at 1 and 3 mo and 0.06 at 6 mo of age compared with children in the IFA group. Supplementation reduced the prevalence of stunting at 1 (RR: 0.95; 95% CI: 0.92, 0.98) and 3 (RR: 0.91; 95% CI: 0.88, 0.94) mo of age. Differences between groups were absent by 6, 12, and 24 mo of age, when nearly 50% of children had stunted growth. Ponderal and linear growth velocities were somewhat slower from 3 to 12 mo of age in the MM group than in the IFA group, but not from 12 to 24 mo of age. There was no difference between groups on composite scores of cognition, language, and motor performance at 24 mo of age.

#### **CONCLUSIONS:**

**In this Bangladeshi trial, maternal pre- and postnatal MM supplementation resulted in improvements in LAZ and reduction in stunting through 3 mo of age, but not thereafter and had no impact on cognitive and motor function at 2 y.**

Free access: <http://ajcn.nutrition.org/content/104/4/1175.long>

[BMC Pregnancy Childbirth.](#) 2016 Aug 12;16:220. doi: 10.1186/s12884-016-1011-z.



**Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review.**

Veena SR<sup>1</sup>, Gale CR<sup>2,3</sup>, Krishnaveni GV<sup>4</sup>, Kehoe SH<sup>2</sup>, Srinivasan K<sup>5</sup>, Fall CH<sup>2</sup>.

**BACKGROUND:**

The mother is the only source of nutrition for fetal growth including brain development. Maternal nutritional status (anthropometry, macro- and micro-nutrients) before and/or during pregnancy is therefore a potential predictor of offspring cognitive function. The relationship of maternal nutrition to offspring cognitive function is unclear. This review aims to assess existing evidence linking maternal nutritional status with offspring cognitive function.

**METHODS:**

Exposures considered were maternal BMI, height and weight, micronutrient status (vitamins D, B12, folate and iron) and macronutrient intakes (carbohydrate, protein and fat). The outcome was any measure of cognitive function in children aged <18 years. We considered observational studies and trials with allocation groups that differed by single nutrients. We searched Medline/PubMed and the Cochrane Library databases and reference lists of retrieved literature. Two reviewers independently extracted data from relevant articles. We used methods recommended by the Centre for Reviews and Dissemination, University of York and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

**RESULTS:**

Of 16,143 articles identified, 38 met inclusion criteria. Most studies were observational, and from high-income settings. There were few randomized controlled trials. There was consistent evidence linking maternal obesity with lower cognitive function in children; low maternal BMI has been inadequately studied. Among three studies of maternal vitamin D status, two showed lower cognitive function in children of deficient mothers. One trial of folic acid supplementation showed no effects on the children's cognitive function and evidence from 13 observational studies was mixed. Among seven studies of maternal vitamin B12 status, most showed no association, though two studies in highly deficient populations suggested a possible effect. Four out of six observational studies and two trials (including one in an Iron deficient population) found no association of maternal iron status with offspring cognitive function. One trial of maternal carbohydrate/protein supplementation showed no effects on offspring cognitive function.

**CONCLUSIONS:**

**Current evidence that maternal nutritional status during pregnancy as defined by BMI, single micronutrient studies, or macronutrient intakes influences offspring cognitive function is inconclusive.** There is a need for more trials especially in populations with high rates of maternal undernutrition.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4982007/>

J Nutr. 2017 Jun;147(6):1094-1103. doi: 10.3945/jn.116.241042. Epub 2017 Apr 26.

**Combined Vitamin B-12 and Balanced Protein-Energy Supplementation Affect Homocysteine Remethylation in the Methionine Cycle in Pregnant South Indian Women of Low Vitamin B-12 Status.**

Devi S<sup>1</sup>, Mukhopadhyay A<sup>1</sup>, Dwarkanath P<sup>1</sup>, Thomas T<sup>2</sup>, Crasta J<sup>3</sup>, Thomas A<sup>4</sup>, Sheela CN<sup>4</sup>, Hsu JW<sup>5</sup>, Tang GJ<sup>5</sup>, Jahoor F<sup>5</sup>, Kurpad AV<sup>6</sup>.

**Background:** Low-quality dietary protein intake and vitamin B-12 deficiency could interact to decrease methionine transmethylation and remethylation rates during pregnancy and may affect epigenetic modifications of the fetal genome.



**Objective:** The objective of this randomized, partially open-labeled intervention trial was to examine **the effect of supplemental high-quality protein and vitamin B-12 on third-trimester methionine kinetics in pregnant Indian women with a low vitamin B-12 status.**

**Methods:** Pregnant women with low serum vitamin B-12 concentrations ( $<200$  pmol/L) were randomly assigned to 1 of 3 groups: the first group received balanced protein-energy supplementation of 500 mL milk/d plus a 10- $\mu$ g vitamin B-12 tablet/d (M+B-12 group;  $n = 30$ ), the second group received milk (500 mL/d) plus a placebo tablet (M+P group;  $n = 30$ ), and the third group received a placebo tablet alone (P group;  $n = 33$ ). Third-trimester fasting plasma amino acid kinetics were measured by infusing 1- $^{13}$ C-methyl- $^2$ H $_3$ -methionine, ring- $^2$ H $_5$ -phenylalanine, ring- $^2$ H $_4$ -tyrosine, 1- $^{13}$ C-glycine, and 2,3,3- $^2$ H $_3$ ,  $^{15}$ N-serine in a subset of participants. Placental mRNA expression of genes involved in methionine pathways, placental long interspersed nuclear elements 1 (LINE-1) methylation, and promoter methylation levels of vascular endothelial growth factor (*VEGF*) were analyzed.

**Results:** Remethylation rates in the M+B-12, M+P, and P groups were  $5.1 \pm 1.7$ ,  $4.1 \pm 1.0$ , and,  $5.0 \pm 1.4$   $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , respectively ( $P = 0.057$ ), such that the percentage of transmethylation remethylated to methionine tended to be higher in the M+B-12 group ( $49.5\% \pm 10.5\%$ ) than in the M+P group ( $42.3\% \pm 8.4\%$ ;  $P = 0.053$ ) but neither differed from the P group ( $44.2\% \pm 8.1\%$ ;  $P > 0.1$ ). Placental mRNA expression, LINE-1, and *VEGF* promoter methylation did not differ between groups.

**Conclusions:** Combined vitamin B-12 and balanced protein-energy supplementation increased the homocysteine remethylation rate in late pregnancy. Thus, vitamin B-12 along with balanced protein-energy supplementation is critical for optimal functioning of the methionine cycle in the third trimester of pregnancy in Indian women with low serum vitamin B-12 in early pregnancy.

[Matern Child Nutr.](#) 2017 Apr;13(2). doi: 10.1111/mcn.12325. Epub 2016 Jun 29.

**[Effects of maternal vitamin B12 supplementation on early infant neurocognitive outcomes: a randomized controlled clinical trial.](#)**

[Srinivasan K](#)<sup>1,2</sup>, [Thomas T](#)<sup>3</sup>, [Kapanee AR](#)<sup>4</sup>, [Ramthal A](#)<sup>1</sup>, [Bellinger DC](#)<sup>5</sup>, [Bosch RJ](#)<sup>6</sup>, [Kurpad AV](#)<sup>7,8</sup>, [Duggan C](#)<sup>7,9</sup>.

### Abstract

Maternal nutritional status during pregnancy impacts fetal brain development. Vitamin B12 plays a vital role in neuronal development. However, findings from studies on the association between maternal B12 status and child cognitive functions have been inconsistent. We performed a randomized, placebo-controlled clinical trial of oral B12 supplementation (50  $\mu$ g) beginning at  $<14$  weeks of gestation through a 6-week post-partum. In the present study, we report **the effects of maternal B12 supplementation on cognitive development in infants at 9 months of age on Bayley Scales of Infant Development-III (BSID-III). One hundred eighty-three pregnant women received vitamin B12, and 183 received placebo.** Nine-month BSID-III development score was available in 178 infants. There were no significant differences in maternal sociodemographic characteristics and baseline biochemical measures between infants who underwent BSID-III evaluation and infants who were not evaluated. **There were no significant differences in any of the subscales of BSID-III between infants born to mothers who received B12 supplementation ( $n = 78$ ) vs. placebo ( $n = 100$ ).** On multiple regression analysis, elevated maternal total homocysteine (tHcy) levels adjusted for treatment group, birthweight, parity, income and home environment at second trimester of pregnancy were significantly negatively associated with expressive language ( $\beta = 3.13$  points,  $P < 0.001$ ), and in third trimester of pregnancy with expressive language ( $\beta = -2.29$  points,  $P < 0.001$ ) and fine motor ( $\beta = -1.41$  points,  $P = 0.005$ ) domains of BSID-III. While no significant effects of

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maternal B12 supplementation were seen on cognitive development in infants at 9 months of age, elevated maternal tHcy levels were associated with poorer cognitive performance in some of the subdomains of BSID-III. In pregnant women with elevated tHcy levels and or B12 deficiencies, it may be worthwhile to study the impact of longer term maternal supplementation on infant cognitive outcomes.

*J Nutr.* 2016 Dec;146(12):2520-2529. Epub 2016 Oct 19.

### **A Prenatal Multiple Micronutrient Supplement Produces Higher Maternal Vitamin B-12 Concentrations and Similar Folate, Ferritin, and Zinc Concentrations as the Standard 60-mg Iron Plus 400-µg Folic Acid Supplement in Rural Bangladeshi Women.**

*Ziaei S<sup>1</sup>, Rahman A<sup>2</sup>, Raqib R<sup>2</sup>, Lönnerdal B<sup>3</sup>, Ekström EC<sup>4</sup>.*

#### **BACKGROUND:**

The effects of prenatal food and micronutrient supplementation on maternal micronutrient status are not well known.

#### **OBJECTIVE:**

We compared the efficacy and effectiveness of 3 different micronutrient supplements on maternal micronutrient status when combined with food supplementation.

#### **METHODS:**

**In the MINIMat (Maternal and Infant Nutrition Intervention, Matlab) trial in Bangladesh, 4436 pregnant women were randomly assigned to daily intake of 3 types of micronutrient capsules: 30 mg Fe and 400 µg folic acid (Fe30F), 60 mg Fe and 400 µg folic acid (Fe60F), or multiple micronutrient supplements (MMNs) combined with early (week 9 of pregnancy) or usual (week 20 of pregnancy) food supplementation in a 2 by 3 factorial design.** Plasma concentrations of vitamin B-12, folate, ferritin, and zinc were analyzed before the start of micronutrient supplementation (week 14) and at week 30 of pregnancy in 641 randomly selected women. An electronic monitoring device was used to measure the number of capsules taken. The effectiveness of food and micronutrient regimens as well as efficacy per capsule in maternal micronutrient status were analyzed by ANOVA and general linear models.

#### **RESULTS:**

**At week 30 of pregnancy, women in the MMN group had higher geometric mean concentrations of vitamin B-12 than women in the Fe60F group (119 compared with 101 pmol/L, respectively);** no other differences in effectiveness of micronutrient and food regimens were observed. A dose-response relation between the number of capsules taken and concentrations of folate and ferritin was observed for all micronutrient supplements. Fe30F had lower efficacy per capsule in increasing ferritin concentrations within the first tertile of capsule intake than did Fe60F and MMNs. Because ferritin reached a plateau for all types of micronutrient supplements, there was no difference between the regimens in their effectiveness.

#### **CONCLUSION:**

**Compared with Fe60F, MMNs produced higher maternal vitamin B-12 and similar ferritin and folate concentrations in Bangladeshi women.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5118763/>

*J Nutr.* 2017 Jun;147(6):1200-1207. doi: 10.3945/jn.116.241968. Epub 2017 Apr 19.

### **An Animal-Source Food Supplement Increases Micronutrient Intakes and Iron Status among Reproductive-Age Women in Rural Vietnam.**

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**Background:** Few studies have examined the impact of local animal-source foods (ASFs) on the nutritional status of reproductive-age women in developing countries.

**Objective:** We hypothesized that a midmorning snack of local ASF for 6 mo would reduce dietary micronutrient deficiencies [usual intake less than the estimated average requirement (EAR)] and improve blood biomarkers of iron, zinc, and vitamins A and B-12 status among nonpregnant, reproductive-age women in rural Vietnam.

**Methods:** One hundred seventeen women, 18-30 y old, were randomly assigned to receive either an ASF (mean: 144 kcal, 8.9 mg Fe, 2.7 mg Zn, 1050 µg retinoic acid equivalent vitamin A, and 5.5 µg vitamin B-12) or a control snack (mean: 150 kcal, 2.0 mg Fe, 0.9 mg Zn, 0 µg retinoic acid equivalent vitamin A, and 0 µg vitamin B-12) 5 d/wk for 6 mo. Usual nutrient intakes were estimated by repeated 24-h dietary recalls. Blood samples were collected at baseline and 3 and 6 mo. Because of the relation between nutritional status and inflammation, serum C-reactive protein,  $\alpha$ -1-acid-glycoprotein, and urinary tract infections (UTIs) were also monitored.

**Results:** Eighty-nine women (47 in the ASF group and 42 controls) completed the study. **In the ASF group, intakes of iron and vitamins A and B-12 below the EAR were eliminated, and the prevalence of a low zinc intake was reduced to 9.6% compared with 64.7% in controls ( $P < 0.001$ ).** At 6 mo, a modest increase ( $P < 0.05$ ) in hemoglobin and iron status occurred in the ASF group compared with the control group, but plasma zinc, retinol, and serum vitamin B-12 concentrations did not differ. UTI relative risk was 3.9 ( $P < 0.05$ ) among women assigned to the ASF group who had a low whole-body iron status at baseline.

**Conclusions:** Adding a small amount of locally produced ASF to the diets of reproductive-age Vietnamese women improved micronutrient intakes and iron status. However, the increased UTI incidence in women in the ASF group with initially lower iron stores warrants further investigation.

[J Nutr.](#) 2017 Apr;147(4):697-705. doi: 10.3945/jn.116.242909. Epub 2017 Mar 8.

### Maternal Supplementation with Small-Quantity Lipid-Based Nutrient Supplements Compared with Multiple Micronutrients, but Not with Iron and Folic Acid, Reduces the Prevalence of Low Gestational Weight Gain in Semi-Urban Ghana: A Randomized Controlled Trial.

[Adu-Afarwuah S](#)<sup>1</sup>, [Lartey A](#)<sup>2</sup>, [Okronipa H](#)<sup>2</sup>, [Ashorn P](#)<sup>3</sup>, [Ashorn U](#)<sup>3</sup>, [Zeilani M](#)<sup>4</sup>, [Arimond M](#)<sup>5</sup>, [Vosti SA](#)<sup>6</sup>, [Dewey KG](#)<sup>5</sup>.

#### **Abstract**

**Background:** It is unclear whether maternal supplementation with **small-quantity lipid-based nutrient supplements** (SQ-LNSs; 118 kcal/d) affects maternal weight.

**Objective:** We compared several secondary anthropometric measures between 3 groups of women in the iLiNS (International Lipid-based Nutrient Supplements)-DYAD trial in Ghana.

**Methods:** Women ( $n = 1320$ ;  $<20$  wk of gestation) were randomly assigned to receive 60 mg Fe + 400 µg folic acid/d (IFA), 18 vitamins and minerals/d [multiple micronutrients (MMNs)], or 20 g SQ-LNSs with 22 micronutrients/d (LNS) during pregnancy and a placebo (200 mg Ca/d), MMNs, or SQ-LNSs, respectively, for 6 mo postpartum. Weight, midupper arm circumference (MUAC), and triceps skinfold (TSF) thickness at 36 wk of gestation and 6 mo postpartum were analyzed, as were changes from estimated prepregnancy values. We assessed the adequacy of estimated gestational weight gain (GWG) by using Institute of Medicine (IOM) and International Fetal and Newborn Growth Standards for the 21st Century (INTERGROWTH-21st) guidelines.

**Results:** The estimated prepregnancy prevalence of overweight or obesity was 38.5%. By 36 wk of gestation, women ( $n = 1015$ ) had a mean  $\pm$  SD weight gain of  $7.4 \pm 3.7$  kg and changes of -

1.0 ± 1.7 cm in MUAC and -2.8 ± 4.1 mm in TSF thickness. The LNS group had a lower prevalence of inadequate GWG on the basis of IOM guidelines (57.4%) than the MMN (67.2%) but not the IFA (63.1%) groups ( $P = 0.030$ ), whereas the prevalence of adequate (26.9% overall) and excessive (10.4% overall) GWG did not differ by group. The percentages of normal-weight women (in kg/m<sup>2</sup>: 18.5 < body mass index < 25.0;  $n = 754$ ) whose GWG was less than the third centile of the INTERGROWTH-21st standards were 23.0%, 28.7%, and 28.5% for the LNS, MMN, and IFA groups, respectively ( $P = 0.36$ ). At 6 mo postpartum, the prevalence of overweight or obesity was 45.3%, and the risk of becoming overweight or obese did not differ by group.

Conclusion: SQ-LNS supplementation is one potential strategy to address the high prevalence of inadequate GWG in women in settings similar to Ghana, without increasing the risk of excessive GWG.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5368579/>

## Meningitis and encephalitis

*Pediatr Infect Dis J.* 2017 Jun;36(6):556-559. doi: 10.1097/INF.0000000000001513.

### **Role of Rifampin in Reducing Inflammation and Neuronal Damage in Childhood Bacterial Meningitis: A Pilot Randomized Controlled Trial.**

Uppal L<sup>1</sup>, Singhi S, Singhi P, Aggarwal R.

#### **BACKGROUND**

Treatment of acute bacterial meningitis in children with bactericidal antibiotics causes cell wall lysis and a surge in inflammatory cascade, which in turn contributes to neuronal damage and morbidity. Pretreatment with a nonbacteriolytic antibiotic, such as rifampin, has been shown to attenuate the inflammatory response in experimental models of bacterial meningitis. In a pilot study, in children with bacterial meningitis, we have studied markers of inflammatory response and neuronal damage in 2 groups of children with bacterial meningitis; one group received rifampin pretreatment with ceftriaxone and the other group received ceftriaxone alone.

#### **PATIENTS AND METHODS**

**Forty children with bacterial meningitis, who were 3 months to 12 years of age, were randomly assigned to receive either a single dose rifampin (20 mg/kg) 30 minutes before ceftriaxone or ceftriaxone alone was given.** The primary outcome variables were cerebrospinal fluid (CSF) concentrations of tumor necrosis factor alpha (TNF $\alpha$ ), S100B and neuron-specific enolase on day 1 and day 5, and secondary outcome variables were the values of TNF $\alpha$  and interleukin 6 in serum on day 1 and day 5; hearing and neurologic sequelae at 3 months after recovery from the illness.

#### **RESULTS**

Children in rifampin pretreatment group had significantly lower CSF TNF $\alpha$  concentrations [median (interquartile range [IQR]): 15.5 (7.2-22.0) vs. 53.0 (9.0-87.5) pg/mL,  $P = 0.019$ ] and S100B [median (IQR): 145.0 (54.7-450.0) vs. 447.5 (221.0-804.6) pg/mL,  $P = 0.033$ ] on day 1 and S100B [median (IQR): 109.7 (64.0-287.0) vs. 322 (106.7-578.0) pg/mL,  $P = 0.048$ ] and neuron-specific enolase [median (IQR): 8.6 (5-14.75) vs. 18.2 (7.0-28.75) ng/mL,  $P = 0.035$ ] on day 5 when compared with ceftriaxone alone group. The rifampin-treated group also had reduced morbidity and neurologic sequelae; however, these were not statistically significant.

#### **CONCLUSIONS:**

**Pretreatment with single dose rifampin 30 minutes before ceftriaxone administration reduced the CSF concentrations of markers of inflammation and neuronal damage in children with bacterial meningitis.**

## Comment

*The non-bacteriolytic but bactericidal antibiotics rifampicin, clindamycin and aminoglycosides kill bacteria without releasing high quantities of proinflammatory cell wall components.*

## Mobile phone technology

[BMC Infect Dis.](#) 2016 Nov 24;16(1):701.

[Community-based interventions to enhance knowledge, protective attitudes and behaviors towards canine rabies: results from a health communication intervention study in Guangxi, China.](#)

[Wu H<sup>1</sup>](#), [Chen J<sup>2</sup>](#), [Zou L<sup>3</sup>](#), [Zheng L<sup>3</sup>](#), [Zhang W<sup>2</sup>](#), [Meng Z<sup>4</sup>](#), [Magalhaes RJ<sup>5,6</sup>](#), [Wang Y<sup>7</sup>](#), [Kang J<sup>7</sup>](#), [Sun X<sup>7</sup>](#).

### BACKGROUND:

In China canine rabies poses a serious public health problem in that human mortality ranks the second highest globally. While rabies health education interventions are advocated by WHO to be critical components of modern rabies control and prevention programs, available studies have not adequately investigated the relative efficacy of their implementation in at-risk populations. This study aims to measure and compare the effect on knowledge and protective behavior towards rabies of health education interventions that include a novel Short Messaging Service via cell phone (SMS) and rabies health information sessions (IS).

### METHODS:

The study used a between-subject design involving repeated measures of rabies-related KAP (knowledge, attitude and practice). A total of 350 randomly selected villagers were randomly allocated into three intervention (SMS, IS and SMS + IS) and one control group. The content of SMS and IS covered topics about rabies prevention and route of transmission. **The SMS intervention consisted of ten separate messages delivered three times two weeks after the pretest; the IS intervention was conducted once immediately after the pretest.** A validated questionnaire was used to capture demographic information and KAP information. Ordinary Least Squares regression was used to contrast the effects of interventions.

### RESULTS:

**Our results indicate that overall SMS outperforms IS at improving knowledge and protective behavior against rabies.** Our results suggest that a combined intervention of SMS and IS can result in higher scores than any of the two in isolation. The impact of SMS, IS and SMS + IS is greatest on knowledge, followed by attitude and practice scores.

### CONCLUSION:

This study demonstrated that health communication modes based on SMS, IS and a combination of the two are all effective to improve rabies-related KAP in the short term. These findings highlight the potential usefulness of SMS as an additional tool for public health communication and promotion; further studies are needed to investigate the long term benefits of these interventions on the reduction of dog bites and resulting human rabies incidence.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5121978/>

[Am J Public Health.](#) 2016 Jul;106(7):1256-62. doi: 10.2105/AJPH.2016.303140. Epub 2016 Apr 14.



**Impact of Text Message Reminders on Caregivers' Adherence to a Home Fortification Program Against Child Anemia in Rural Western China: A Cluster-Randomized Controlled Trial.**

[Zhou H<sup>1</sup>](#), [Sun S<sup>1</sup>](#), [Luo R<sup>1</sup>](#), [Sylvia S<sup>1</sup>](#), [Yue A<sup>1</sup>](#), [Shi Y<sup>1</sup>](#), [Zhang L<sup>1</sup>](#), [Medina A<sup>1</sup>](#), [Rozelle S<sup>1</sup>](#).

**OBJECTIVES:**

To test whether text message reminders sent to caregivers improve the effectiveness of a home micronutrient fortification program in western China.

**METHODS:**

We carried out a cluster-randomized controlled trial in 351 villages (clusters) in Shaanxi Province in 2013 and 2014, enrolling children aged 6 to 12 months. We randomly assigned each village to 1 of 3 groups: free delivery group, text messaging group, or control group. We collected information on compliance with treatments and hemoglobin concentrations from all children at baseline and 6-month follow-up. We estimated the intent-to-treat effects on compliance and child anemia using a logistic regression model.

**RESULTS:**

There were 1393 eligible children. We found that assignment to the text messaging group led to an increase in full compliance (marginal effect = 0.10; 95% confidence interval [CI] = 0.03, 0.16) compared with the free delivery group and decrease in the rate of anemia at end line relative to the control group (marginal effect = -0.07; 95% CI = -0.12, -0.01), but not relative to the free delivery group (marginal effect = -0.03; 95% CI = -0.09, 0.03).

**CONCLUSIONS:**

**Text messages improved compliance of caregivers to a home fortification program and children's nutrition.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4984765/>

[BMC Public Health](#). 2016 Aug 31;16:909. doi: 10.1186/s12889-016-3549-0.

**Effectiveness of a smartphone app on improving immunization of children in rural Sichuan Province, China: a cluster randomized controlled trial.**

[Chen L<sup>1</sup>](#), [Du X<sup>1</sup>](#), [Zhang L<sup>2</sup>](#), [van Velthoven MH<sup>3</sup>](#), [Wu Q<sup>1</sup>](#), [Yang R<sup>4</sup>](#), [Cao Y<sup>4</sup>](#), [Wang W<sup>1</sup>](#), [Xie L<sup>1</sup>](#), [Rao X<sup>1</sup>](#), [Zhang Y<sup>5</sup>](#), [Koepsell JC<sup>6</sup>](#).

**BACKGROUND:**

The aim of this study was to assess the effectiveness of an EPI smartphone application (EPI app) on improving vaccination coverage in rural Sichuan Province, China.

**METHODS:**

This matched-pair cluster randomized controlled study included 32 village doctors, matched in 16 pairs, and took place from 2013 to 2015. **Village doctors in the intervention group used the EPI app and reminder text messages while village doctors in the control group used their usual procedures and text messages.** The primary outcome was full vaccination coverage with all five vaccines (1 dose of BCG, 3 doses of hepatitis B, 3 doses of OPV, 3 doses of DPT and 1 dose of measles vaccine), and the secondary outcome was coverage with each dose of the five individual vaccines. We also conducted qualitative interviews with village doctors to understand perceptions on using the EPI app and how this changed their vaccination work.

**RESULTS:**

**The full vaccination coverage increased statistically significant from baseline to end-line in both the intervention (67 % [95 % CI:58-75 %] to 84 % [95 % CI:76-90 %], P = 0.028) and control group (71 % [95 % CI:62-79 %] to 82 % [95 % CI:74-88 %], P = 0.014).** The intervention group had higher increase in full vaccination coverage from baseline to end-line



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compared to the control group (17 % vs 10 %), but this was not statistically significant ( $P = 0.164$ ). **Village doctors found it more convenient to use the EPI app to manage child vaccination and also reported saving time by looking up information of caregivers and contacting caregivers for overdue vaccinations quicker.** However, village doctors found it hard to manage children who migrated out of the counties.

### CONCLUSIONS:

This study showed that an app and text messages can be used by village doctors to improve full vaccination coverage, though no significant increase in vaccination coverage was found when assessing the effect of the app on its own. Village doctors using EPI app reported having improved their working efficiency of managing childhood vaccination. Future studies should be conducted to evaluate the impact of more integrated approach of mHealth intervention on child immunization.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5006404/>

[Int J Gynaecol Obstet.](#) 2016 Jul;134(1):93-8. doi: 10.1016/j.ijgo.2015.12.008. Epub 2016 Apr 8.

### **Effects of postpartum mobile phone-based education on maternal and infant health in Ecuador.**

[Maslowsky J](#)<sup>1</sup>, [Frost S](#)<sup>2</sup>, [Hendrick CE](#)<sup>3</sup>, [Trujillo Cruz FO](#)<sup>4</sup>, [Merajver SD](#)<sup>5</sup>.

### OBJECTIVE:

**To evaluate the effects of a mobile phone-based intervention on postnatal maternal health behavior and maternal and infant health in a middle-income country.**

### METHODS:

A prospective evaluation enrolled consecutive postpartum women at two public hospitals in Quito, Ecuador, between June and August 2012. Inclusion criteria were live birth, no neonatal intensive care admission, and Spanish speaking. Intervention and control groups were assigned via random number generation. **The intervention included a telephone-delivered educational session and phone/text access to a nurse for 30days after delivery.** Maternal and infant health indicators were recorded at delivery and 3months after delivery via chart review and written/telephone-administered survey.

### RESULTS:

Overall, 102 women were assigned to the intervention group and 76 to the control group. **At 3months, intervention participants were more likely to attend the infant's postnatal check-up ( $P=0.022$ ) and to breastfeed exclusively ( $P=0.005$ ), and less likely to feed formula ( $P=0.016$ ).** They used more effective forms of contraception (more implants  $P=0.023$ ; fewer condoms  $P=0.036$ ) and reported fewer infant illnesses ( $P=0.010$ ). There were no differences in maternal acute illness or check-up attendance.

### CONCLUSION:

**Mobile phone-based postnatal patient education is a promising strategy for improving breastfeeding, contraceptive use, and infant health in low-resource settings; different strategies are needed to influence postpartum maternal health behavior.**

[JMIR Res Protoc.](#) 2016 Jul 27;5(3):e158. doi: 10.2196/resprot.5968.

### **MHealth to Improve Measles Immunization in Guinea-Bissau: Study Protocol for a Randomized Controlled Trial.**

[Rossing E](#)<sup>1</sup>, [Ravn H](#), [Batista CS](#), [Rodrigues A](#).

### BACKGROUND:

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Recent studies have revealed a low measles vaccination (MV) rate in the Republic of Guinea-Bissau (West Africa) that has not increased in accordance with the increasing coverage of other vaccinations. Measles is the deadliest of all childhood rash/fever illnesses and spreads easily, implying that if the vaccination coverage is declining there is a significant risk of new measles outbreaks [27]. **Meanwhile, mobile health (mHealth; the use of mobile phones for health interventions) has generated much enthusiasm, and shown potential in improving health service delivery in other contexts.**

### **OBJECTIVE:**

The aim of this study is to evaluate the efficiency of mHealth as a tool for improving MV coverage while contributing to the mHealth evidence base.

### **METHODS:**

This study will take place at three health centers in different regions of Guinea-Bissau. Participants, defined as mothers of the children receiving the MV, will be enrolled when they arrive with their children at the health center to receive the Bacillus Calmette-Guérin vaccination, usually within one month of the child's birth. Enrolment will continue until a study population of 990 children has been reached. The participants will be randomly assigned to a control arm or one of two intervention arms. Each of the three groups will have 330 participants, distributed equally between health centers. Participants in the first intervention arm will receive a scheduled short message service (SMS) text message reminding them of the MV. Participants in the second intervention arm will receive a voice call in addition to the SMS message, while the control arm will receive no interventions. The MV is scheduled to be administered at 9 months of age. Although the vaccine would still be effective after 12 months, local policy in Guinea-Bissau prevents children aged >12 months from receiving the vaccination, and thus the study will follow-up with participants after the children reach 12 months of age. Children who have not yet received the MV will be offered vaccination by the project group.

### **RESULTS:**

The study will analyze the efficiency of the intervention by determining its overall effect on MV coverage and timeliness when children reach 12 months of age. The main analysis will be stratified by intervention group, health center, level of education, ethnic group, and role of the person receiving the text messages (eg, mother, father, other family member). Secondary outcomes include the average number of health center visits (with intention to obtain the MV) required before successful administration.

### **CONCLUSIONS:**

Despite the rapid proliferation of mHealth projects, only a small number have been evaluated in terms of direct links to health outcomes. This gap in knowledge requires solid evidence on which policy-makers can base decisions. This study aims to produce significant knowledge about mHealth implementation within a Sub-Saharan context while creating data-supported evidence.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980551/>

[Trials](#). 2017 Jun 9;18(1):270. doi: 10.1186/s13063-017-1998-0.

[Cluster randomized trial of a mHealth intervention "ImTeCHO" to improve delivery of proven maternal, neonatal, and child care interventions through community-based Accredited Social Health Activists \(ASHAs\) by enhancing their motivation and strengthening supervision in tribal areas of Gujarat, India: study protocol for a randomized controlled trial.](#)

[Modi D<sup>1</sup>](#), [Desai S<sup>2</sup>](#), [Dave K<sup>1</sup>](#), [Shah S<sup>1</sup>](#), [Desai G<sup>1</sup>](#), [Dholakia N<sup>3</sup>](#), [Gopalan R<sup>4</sup>](#), [Shah P<sup>1</sup>](#).

### **BACKGROUND:**

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To facilitate the delivery of proven maternal, neonatal, and child health (MNCH) services, a new cadre of village-based frontline workers, called the Accredited Social Health Activists (ASHAs), was created in 2005 under the aegis of the National Rural Health Mission in India. Evaluations have noted that coverage of selected MNCH services to be delivered by the ASHAs is low. Reasons for low coverage are inadequate supervision and support to ASHAs apart from insufficient skills, poor quality of training, and complexity of tasks to be performed. The proposed study aims to implement and evaluate an innovative intervention based on mobile phone technology (mHealth) to improve the performance of ASHAs through better supervision and support in predominantly tribal and rural communities of Gujarat, India.

### **METHODS/DESIGN:**

This is a two-arm, stratified, cluster randomized trial of 36 months in which the units of randomization will be Primary Health Centers (PHCs). There are 11 PHCs in each arm. The intervention is a newly built mobile phone application used in the public health system and evaluated in three ways: (1) mobile phone as a job aid to ASHAs to increase coverage of MNCH services; (2) mobile phone as a job aid to ASHAs and Auxiliary Nurse Midwives (ANMs) to increase coverage of care among complicated cases by facilitating referrals, if indicated and home-based care; (3) web interface as a job aid for medical officers and PHC staff to improve supervision and support to the ASHA program. Participants of the study are pregnant women, mothers, infants, ASHAs, and PHC staff. Primary outcome measures are a composite index made of critical, proven MNCH services and the proportion of neonates who were visited by ASHAs at home within the first week of birth. Secondary outcomes include coverage of selected MNCH services and care sought by complicated cases. Outcomes will be measured by conducting household surveys at baseline and post-intervention which will be compared with usual practice in the control area, where the current level of services provided by the government will continue. The primary analysis will be intention to treat.

### **DISCUSSION:**

This study will help answer some critical questions about the effectiveness and feasibility of implementing an mHealth solution in an area of MNCH services.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5466719/>

[Contemp Clin Trials](#). 2017 Jun;57:44-50. doi: 10.1016/j.cct.2017.03.007. Epub 2017 Mar 14. **Evaluation of mHealth strategies to optimize adherence and efficacy of Option B+ prevention of mother-to-child HIV transmission: Rationale, design and methods of a 3-armed randomized controlled trial.**

[Drake AL](#)<sup>1</sup>, [Unger JA](#)<sup>2</sup>, [Ronen K](#)<sup>3</sup>, [Matemo D](#)<sup>4</sup>, [Perrier T](#)<sup>5</sup>, [DeRenzi B](#)<sup>6</sup>, [Richardson BA](#)<sup>7</sup>, [Kinuthia J](#)<sup>8</sup>, [John-Stewart G](#)<sup>9</sup>.

### **BACKGROUND:**

Lifelong antiretroviral therapy (ART) (Option B+) is recommended for all HIV-infected pregnant/postpartum women, but high adherence is required to maximize HIV prevention potential and maintain maternal health. Mobile health (mHealth) interventions may provide treatment adherence support for women during, and beyond, the pregnancy and postpartum periods.

### **METHODS AND DESIGN:**

We are conducting an unblinded, triple-arm randomized clinical trial (Mobile WACH X) of one-way short message service (SMS) vs. two-way SMS vs. control (no SMS) to improve maternal ART adherence and retention in care by 2 years postpartum. We will enroll 825 women from Nairobi and Western Kenya. Women in the intervention arms receive weekly, semi-automated motivational and educational SMS and visit reminders via an interactive, human-computer

hybrid communication system. Participants in the two-way SMS arm are also asked to respond to a question related to the message. SMS are based in behavioral theory, are tailored to participant characteristics through SMS tracks, and are timed along the pregnancy/postpartum continuum. After enrollment, follow-up visits are scheduled at 6 weeks; 6, 12, 18, and 24 months postpartum. The primary outcomes, virological failure (HIV viral load  $\geq 1000$  copies/mL), maternal retention in care, and infant HIV infection or death, will be compared in an intent to treat analysis. We will also measure ART adherence and drug resistance.

### DISCUSSION:

Personalized and tailored SMS to support HIV-infected women during and after pregnancy may be an effective strategy to motivate women to adhere to ART and remain in care and improve maternal and infant outcomes.

## Newborn care

[JAMA Pediatr.](#) 2017 Mar 1;171(3):264-270. doi: 10.1001/jamapediatrics.2016.3971.

### Effects of Delayed Umbilical Cord Clamping vs Early Clamping on Anemia in Infants at 8 and 12 Months: A Randomized Clinical Trial.

[Kc A<sup>1</sup>](#), [Rana N<sup>2</sup>](#), [Målvist M<sup>3</sup>](#), [Jarawka Ranneberg L<sup>4</sup>](#), [Subedi K<sup>5</sup>](#), [Andersson O<sup>3</sup>](#).

#### Importance:

Delayed umbilical cord clamping has been shown to improve iron stores in infants to 6 months of age. However, delayed cord clamping has not been shown to prevent iron deficiency or anemia after 6 months of age.

#### Objective:

**To investigate the effects of delayed umbilical cord clamping, compared with early clamping, on hemoglobin and ferritin levels at 8 and 12 months of age in infants at high risk for iron deficiency anemia.**

#### Design, Setting, and Participants:

This randomized clinical trial included 540 late preterm and term infants born vaginally at a tertiary hospital in Kathmandu, Nepal, from October 2 to November 21, 2014. Follow-up included blood levels of hemoglobin and ferritin at 8 and 12 months of age. Follow-up was completed on December 11, 2015. Analysis was based on intention to treat.

#### Interventions:

Infants were randomized to delayed umbilical cord clamping ( $\geq 180$  seconds after delivery) or early clamping ( $\leq 60$  seconds after delivery).

#### Main Outcomes and Measures:

Main outcomes included hemoglobin and anemia levels at 8 months of age with the power estimate based on the prevalence of anemia. Secondary outcomes included hemoglobin and anemia levels at 12 months of age and ferritin level, iron deficiency, and iron deficiency anemia at 8 and 12 months of age.

#### Results:

In this study of 540 infants (281 boys [52.0%] and 259 girls [48.0%]; mean [SD] gestational age, 39.2 [1.1] weeks), **270 each were randomized to the delayed and early clamping groups**. At 8 months of age, 212 infants (78.5%) from the delayed group and 188 (69.6%) from the early clamping group returned for blood sampling. **After multiple imputation analysis, infants undergoing delayed clamping had higher levels of hemoglobin (10.4 vs 10.2 g/dL; difference, 0.2 g/dL; 95% CI, 0.1 to 0.4 g/dL).** Delayed cord clamping also reduced the prevalence of anemia (hemoglobin level  $< 11.0$  g/dL) at 8 months in 197 (73.0%) vs 222 (82.2%) infants (relative risk, 0.89; 95% CI, 0.81-0.98; number needed to treat [NNT], 11; 95% CI, 6-54). **At 8 months, the risk for iron deficiency was reduced in the delayed clamping group in**

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60 (22.2%) vs 103 (38.1%) patients (relative risk, 0.58; 95% CI, 0.44-0.77; NNT, 6; 95% CI, 4-13). At 12 months, delayed cord clamping still resulted in a hemoglobin level of 0.3 (95% CI, 0.04-0.5) g/dL higher than in the early cord clamping group and a relative risk for anemia of 0.91 (95% CI, 0.84-0.98), resulting in a NNT of 12 (95% CI, 7-78).

### Conclusions and Relevance:

Delayed cord clamping reduces anemia at 8 and 12 months of age in a high-risk population, which may have major positive effects on infants' health and development

[Resuscitation](#). 2016 Aug;105:79-84. doi: 10.1016/j.resuscitation.2016.05.015. Epub 2016 May 30.

### [Endotracheal suction in term non vigorous meconium stained neonates-A pilot study.](#)

[Nangia S](#)<sup>1</sup>, [Sunder S](#)<sup>2</sup>, [Biswas R](#)<sup>3</sup>, [Saili A](#)<sup>2</sup>.

#### AIM:

To evaluate the effect of 'No endotracheal suction' on occurrence of meconium aspiration syndrome (MAS) and/or all-cause mortality in non-vigorous neonates born through meconium stained amniotic fluid (MSAF).

#### METHODS:

This pilot randomized controlled trial enrolled term non-vigorous neonates ( $\geq 37$  weeks) born through MSAF. Neonates randomized to 'No Endotracheal suction group' ('No ET' Group; n=88) did not undergo endotracheal suction before the definitive steps of resuscitation. Neonates randomized to 'Endotracheal suction group' ('ET' Group; n=87) underwent tracheal suction as part of the initial steps as per the current NRP recommendations. The primary outcome was occurrence of MAS and/or death. Secondary outcome variables were duration and severity of respiratory distress, need for respiratory support, development of hypoxic ischemic encephalopathy (HIE) and duration of oxygen therapy and hospitalization.

#### RESULTS:

Baseline characters including birth weight and gestational age were similar between the two groups. MAS was present in 23 (26.1%) vs. 28 (32.2%) neonates in 'No ET' and 'ET' groups respectively (OR 0.4 (0.12-1.4); p=0.14) with 4 (4.6%) and 9 (10.34%) deaths amongst these neonates with MAS in respective groups (OR 0.75 (0.62-1.2); p=0.38). Other parameters like severity and duration of respiratory distress, need for respiratory support, incidence of HIE, duration of oxygen therapy and duration of hospitalization were comparable.

#### CONCLUSION:

This study demonstrates that it is feasible to randomize non-vigorous infants born through meconium stained liquor to receive or not receive endotracheal suction. There is a need for a multi-center trial to address whether the current practices and guidelines can be justified.

[Glob Health Sci Pract](#). 2017 Jun 27;5(2):232-243. doi: 10.9745/GHSP-D-16-00411. Print 2017 Jun 27.

### [The BetterBirth Program: Pursuing Effective Adoption and Sustained Use of the WHO Safe Childbirth Checklist Through Coaching-Based Implementation in Uttar Pradesh, India.](#)

[Kara N](#), [Firestone R](#), [Kalita T](#), [Gawande AA](#), [Kumar V](#), [Kodkany B](#), [Saurastri R](#), [Pratap Singh V](#), [Maji P](#), [Karlage A](#), [Hirschhorn LR](#), [Semrau KE](#); [BetterBirth Trial Group](#).

#### [Author information](#)

#### Abstract



Shifting childbirth into facilities has not improved health outcomes for mothers and newborns as significantly as hoped. Improving the quality and safety of care provided during facility-based childbirth requires helping providers to adhere to essential birth practices-evidence-based behaviors that reduce harm to and save lives of mothers and newborns. To achieve this goal, we developed the BetterBirth Program, which we tested in a matched-pair, cluster-randomized controlled trial in Uttar Pradesh, India. The goal of this intervention was to improve adoption and sustained use of the World Health Organization Safe Childbirth Checklist (SCC), an organized collection of 28 essential birth practices that are known to improve the quality of facility-based childbirth care. Here, we describe the BetterBirth Program in detail, including its 4 main features: implementation tools, an implementation strategy of coaching, an implementation pathway (Engage-Launch-Support), and a sustainability plan. This coaching-based implementation of the SCC motivates and empowers care providers to identify, understand, and resolve the barriers they face in using the SCC with the resources already available. We describe important lessons learned from our experience with the BetterBirth Program as it was tested in the BetterBirth Trial. For example, the emphasis on relationship building and respect led to trust between coaches and birth attendants and helped influence change. In addition, the cloud-based data collection and feedback system proved a valuable asset in the coaching process. More research on coaching-based interventions is required to refine our understanding of what works best to improve quality and safety of care in various settings. Note: At the time of publication of this article, the results of evaluation of the impact of the BetterBirth Program were pending publication in another journal. After the impact findings have been published, we will update this article with a reference to the impact findings.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5487086/>

[Trials](#). 2016 Dec 7;17(1):576.

**Effectiveness of the WHO Safe Childbirth Checklist program in reducing severe maternal, fetal, and newborn harm in Uttar Pradesh, India: study protocol for a matched-pair, cluster-randomized controlled trial.**

[Semrau KE](#)<sup>1</sup>, [Hirschhorn LR](#)<sup>2</sup>, [Kodkany B](#)<sup>3</sup>, [Spector JM](#)<sup>4</sup>, [Tuller DE](#)<sup>5</sup>, [King G](#)<sup>6</sup>, [Lipsitz S](#)<sup>7</sup>, [Sharma N](#)<sup>8</sup>, [Singh VP](#)<sup>8</sup>, [Kumar B](#)<sup>8</sup>, [Dhingra-Kumar N](#)<sup>9</sup>, [Firestone R](#)<sup>10</sup>, [Kumar V](#)<sup>11</sup>, [Gawande AA](#)<sup>12</sup>.

**BACKGROUND:**

Effective, scalable strategies to improve maternal, fetal, and newborn health and reduce preventable morbidity and mortality are urgently needed in low- and middle-income countries. Building on the successes of previous checklist-based programs, the **World Health Organization (WHO) and partners led the development of the Safe Childbirth Checklist (SCC), a 28-item list of evidence-based practices linked with improved maternal and newborn outcomes.** Pilot-testing of the Checklist in Southern India demonstrated dramatic improvements in adherence by health workers to essential childbirth-related practices (EBPs). The BetterBirth Trial seeks to measure the effectiveness of SCC impact on EBPs, deaths, and complications at a larger scale.

**METHODS/DESIGN:**

This matched-pair, cluster-randomized controlled, adaptive trial will be conducted in 120 facilities across 24 districts in Uttar Pradesh, India. Study sites, identified according to predefined eligibility criteria, were matched by measured covariates before randomization. The intervention, the SCC embedded in a quality improvement program, consists of leadership engagement, a 2-day educational launch of the SCC, and support through placement of a trained peer "coach" to provide supportive supervision and real-time data feedback over an 8-month



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period with decreasing intensity. A facility-based childbirth quality coordinator is trained and supported to drive sustained behavior change after the BetterBirth team leaves the facility. Study participants are birth attendants and women and their newborns who present to the study facilities for childbirth at 60 intervention and 60 control sites. The primary outcome is a composite measure including maternal death, maternal severe morbidity, stillbirth, and newborn death, occurring within 7 days after birth. The sample size ( $n = 171,964$ ) was calculated to detect a 15% reduction in the primary outcome. Adherence by health workers to EBPs will be measured in a subset of births ( $n = 6000$ ). The trial will be conducted in close collaboration with key partners including the Governments of India and Uttar Pradesh, the World Health Organization, an expert Scientific Advisory Committee, an experienced local implementing organization (Population Services International, PSI), and frontline facility leaders and workers.

### DISCUSSION:

If effective, the WHO Safe Childbirth Checklist program could be a powerful health facility-strengthening intervention to improve quality of care and reduce preventable harm to women and newborns, with millions of potential beneficiaries.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142140/>

### Comment

*Information on the WHO Safe Birth Checklist is available at this URL:*

<http://www.who.int/patientsafety/implementation/checklists/childbirth/en/>

[J Matern Fetal Neonatal Med.](#) 2016 Sep;29(18):3009-13. doi: 10.3109/14767058.2015.1113520. Epub 2015 Nov 30.

### [Prebiotics for the management of hyperbilirubinemia in preterm neonates.](#)

[Armanian AM](#)<sup>1,2</sup>, [Barekatian B](#)<sup>1,2</sup>, [Hoseinzadeh M](#)<sup>1</sup>, [Salehimehr N](#)<sup>3</sup>.

### OBJECTIVE:

We evaluated if prebiotics have benefits for the management of hyperbilirubinemia in preterm neonates.

### METHODS:

Preterm neonates were entered into the study when enteral feeding volume met 30 mL/kg/day. They randomly received a **mixture of short-chain galacto-oligosaccharids/long-chain fructo-oligosaccharids or distilled water (placebo) for 1 week**. Total serum bilirubin level was measured by transcutaneous bilirubinometry. Stool frequency and meeting full enteral feeding during the study period were considered as secondary outcomes.

### RESULTS:

Twenty-five neonates in each group completed the trial. Bilirubin level was decreased with the prebiotic ( $-1.3 \pm 1.8$  mg/dL,  $p = 0.004$ ), but not placebo ( $-0.1 \pm 3.3$  mg/dL,  $p = 0.416$ ). Peak bilirubin level was lower with the prebiotic than placebo ( $8.3 \pm 1.7$  versus  $10.1 \pm 2.2$  mg/dL,  $p = 0.003$ ). Stool frequency was increased with the prebiotic ( $0.7 \pm 1.9$  defecation/day,  $p = 0.014$ ), but not with placebo ( $0.6 \pm 1.5$  defecation/day,  $p = 0.133$ ). Average stool frequency ( $2.4 \pm 0.4$  versus  $1.9 \pm 0.5$  defecation/day,  $p = 0.003$ ) and frequently of meeting full enteral feeding (60% versus 16%,  $p = 0.002$ ) were higher with the prebiotic than placebo.

### CONCLUSIONS:

**Prebiotic oligosaccharides increase stool frequency, improve feeding tolerance and reduce bilirubin level in preterm neonates and therefore can be efficacious for the management of neonatal hyperbilirubinemia.**

## Comment

*Breast milk contains oligosaccharides including galacto-oligosaccharides and long-chain fructo-oligosaccharides. These influence the intestinal microbial flora. The earlier trial of pre-biotics in preterm babies which also showed an effect on lowering bilirubin (Bisceglia M, et al. Acta Paediatrica 2009) was in formula fed babies. However supplementation would not be needed (or would be expected to have a more limited effect) in breast fed babies who already receive these pre-biotics naturally.*

[Midwifery](#). 2016 Nov;42:21-28. doi: 10.1016/j.midw.2016.09.006. Epub 2016 Sep 15.

### **Development and evaluation of a newborn care education programme in primiparous mothers in Nepal.**

[Shrestha S](#)<sup>1</sup>, [Adachi K](#)<sup>2</sup>, [Petrini MA](#)<sup>3</sup>, [Shrestha S](#)<sup>4</sup>, [Rana Khagi B](#)<sup>5</sup>.

#### **BACKGROUND:**

the health and survival of newborns depend on high levels of attention and care from caregivers. The growth and development of some infants are unhealthy because of their mother's or caregiver's lack of knowledge or the use of inappropriate or traditional child-rearing practices that may be harmful.

#### **OBJECTIVE:**

**to develop a newborn care educational programme and evaluate its impact on infant and maternal health in Nepal.**

#### **DESIGN:**

a randomised controlled trial.

#### **PARTICIPANTS:**

one hundred and forty-three mothers were randomly assigned to the intervention (n=69) and control (n=74) groups. Eligible participants were primiparous mothers who had given birth to a single, full-term, healthy infant, and were without a history of obstetric, medical, or psychological problems.

#### **METHODS:**

prior to being discharged from the postnatal unit, the intervention group received our structured newborn care education programme, which consisted of **one-on-one educational sessions lasting 10-15minutes each and one postpartum follow-up telephone support within two weeks after discharge, in addition to the hospital's routine general newborn care education.** The control group received only the regular general newborn care education. Outcomes were measured by using Newborn care Knowledge Questionnaires, Karitane Parenting Confidence Scale, State-Trait Anxiety Inventory for Adults and infant health and care status.

#### **FINDINGS:**

**the number of mothers attending the health centre due to the sickness of their babies was significantly decreased in the intervention group compared to the control group.** Moreover, **the intervention group had significant increases in newborn care knowledge and confidence, and decreases in anxiety, compared with the control group.**

#### **CONCLUSIONS:**

the structured newborn care education programme enhanced the infant and mother health. Moreover, it increased maternal knowledge of newborn care and maternal confidence; and reduced anxiety in primiparous mothers. Thus, this educational programme could be integrated into routine educational programs to promote maternal and infant well-being in Nepalese society.

## Low birth weight and prematurity

[J Matern Fetal Neonatal Med.](#) 2017 Jun 30;1-18. doi: 10.1080/14767058.2017.1342797. [Epub ahead of print]

### **Role of amino acid supplementation in the prevention of necrotizing enterocolitis in preterm neonates - a review of current evidences.**

[Garg BD<sup>1</sup>](#), [Kabra NS<sup>1</sup>](#).

#### **Abstract**

#### **BACKGROUND:**

Necrotizing enterocolitis (NEC) is one of the most common acute and fatal gastrointestinal emergency in very low birth weight (VLBW) preterm neonates with mortality range from 15 to 30%. NEC is likely due to multifactorial process such as oxidative injury, ischemic necrosis, and over-reactive inflammatory response to intestinal microbes.

#### **AIMS:**

**To evaluate the role of amino acid supplementation for reduction of neonatal NEC in preterm neonates.**

#### **METHOD:**

The literature search was done for various randomized control trial (RCT) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, Web of Science, Scopus, Index Copernicus, African Index Medicus (AIM), Thomson Reuters (ESCI), Chemical Abstracts Service (CAS) and other database.

#### **RESULTS:**

This review included 15 RCTs that fulfilled inclusion criteria. **The total neonates enrolled in these different RCT are 3424 (amino acid group 1711 and control 1713). Almost all participating neonates were of VLBW or extremely low birth weight (ELBW).** In two trials, birth weight was between 1500-2000 grams. The intervention was started within first few days after birth and continued up to 30th day of postnatal age in most of the trials. In two trials, intervention was continued up to 120th day of postnatal age. Arginine, glutamine and N-acetyl cysteine (NAC) were used at the dose of 1.5 mol/kg/day (261 mg/kg/day), 0.3 grams/kg/day and 16-32 mg/kg/day, respectively.

#### **CONCLUSION:**

**Role of amino acid in the prevention of neonatal NEC is not exclusively supported by the current evidence.** Only three studies were able to show reduction in the incidence of NEC with amino acid supplementation (arginine, glutamine), and the remaining studies did not report any positive effect. Amino acid supplementation was not associated with significant reduction in mortality due to any causes. **However, arginine supplementation was associated with significant reduction in mortality due to NEC.** Two studies on glutamine were reported significant reduction in the incidence of invasive infection. Only one study reported significant positive effects on growth parameters and less time to reach full enteral feeds. None of the studies showed any effect on the duration of hospital stay.

[Trials.](#) 2017 Jun 7;18(1):262. doi: 10.1186/s13063-017-1991-7.

### **Impact of community-initiated Kangaroo Mother Care on survival of low birth weight infants: study protocol for a randomized controlled trial.**

[Mazumder S<sup>1</sup>](#), [Taneja S<sup>1</sup>](#), [Dalpath SK<sup>2</sup>](#), [Gupta R<sup>2</sup>](#), [Dube B<sup>1</sup>](#), [Sinha B<sup>1</sup>](#), [Bhatia K<sup>1</sup>](#), [Yoshida S<sup>3</sup>](#), [Norheim OF<sup>4</sup>](#), [Bahl R<sup>3</sup>](#), [Sommerfelt H<sup>5,6</sup>](#), [Bhandari N<sup>1</sup>](#), [Martines J<sup>4</sup>](#).

#### **BACKGROUND:**

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Around 70% neonatal deaths occur in low birth weight (LBW) babies. Globally, 15% of babies are born with LBW. Kangaroo Mother Care (KMC) appears to be an effective way to reduce mortality and morbidity among LBW babies. KMC comprises of early and continuous skin-to-skin contact between mother and baby as well as exclusive breastfeeding. Evidence derived from hospital-based studies shows that KMC results in a 40% relative reduction in mortality, a 58% relative reduction in the risk of nosocomial infections or sepsis, shorter hospital stay, and a lower risk of lower respiratory tract infections in babies with birth weight <2000 g. There has been considerable interest in KMC initiated outside health facilities for LBW babies born at home or discharged early. Currently, there is insufficient evidence to support initiation of KMC in the community (cKMC). Formative research in our study setting, where 24% of babies are born with LBW, demonstrated that KMC is feasible and acceptable when initiated at home for LBW babies. The aim of this trial is to determine the impact of cKMC on the survival of these babies.

### METHODS/DESIGN:

This randomized controlled trial is being undertaken in the Palwal and Faridabad districts in the State of Haryana, India. Neonates weighing 1500-2250 g identified within 3 days of birth and their mothers are being enrolled. Other inclusion criteria are that the family is likely to be available in the study area over the next 6 months, that KMC was not initiated in the delivery facility, and that the infant does not have an illness requiring hospitalization. Eligible neonates are randomized into intervention and control groups. The intervention is delivered through home visits during the first month of life by study workers with a background and education similar to that of workers in the government health system. An independent study team collects mortality and morbidity data as well as anthropometric measurements during periodic home visits. The primary outcomes of the study are postenrollment neonatal mortality and mortality between enrollment and 6 months of age. The secondary outcomes are breastfeeding practices; prevalence of illnesses and care-seeking practices for the same; hospitalizations; weight and length gain; and, in a subsample, neurodevelopment.

### DISCUSSION:

**This efficacy trial will answer the question whether the benefits of KMC observed in hospital settings can also be observed when KMC is started in the community.** The formative research used for intervention development suggests that the necessary high level of KMC adoption can be reached in the community, addressing a problem that seriously constrained conclusions in the only other trial in which researchers examined the benefits of cKMC.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5463407/>

*Pediatrics*. 2017 Jan;139(1). pii: e20162063. doi: 10.1542/peds.2016-2063. Epub 2016 Dec 12.

### Twenty-year Follow-up of Kangaroo Mother Care Versus Traditional Care.

Charpak N<sup>1</sup>, Tessier R<sup>2</sup>, Ruiz JG<sup>3,4</sup>, Hernandez JT<sup>5</sup>, Uriza F<sup>3,4</sup>, Villegas J<sup>6</sup>, Nadeau L<sup>2</sup>, Mercier C<sup>2</sup>, Maheu F<sup>7</sup>, Marin J<sup>8</sup>, Cortes D<sup>9</sup>, Gallego JM<sup>9</sup>, Maldonado D<sup>5</sup>.

### BACKGROUND AND OBJECTIVES:

Kangaroo mother care (KMC) is a multifaceted intervention for preterm and low birth weight infants and their parents. Short- and mid-term benefits of KMC on survival, neurodevelopment, breastfeeding, and the quality of mother-infant bonding were documented in a randomized controlled trial (RCT) conducted in Colombia from 1993 to 1996. The aim of the present study was to evaluate the persistence of these results in young adulthood.

### METHODS:

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From 2012 to 2014, a total of 494 (69%) of the 716 participants of the original RCT known to be alive were identified; 441 (62% of the participants in the original RCT) were re-enrolled, and results for the 264 participants weighing  $\leq 1800$  g at birth were analyzed. The KMC and control groups were compared for health status and neurologic, cognitive, and social functioning with the use of neuroimaging, neurophysiological, and behavioral tests.

### RESULTS:

**The effects of KMC at 1 year on IQ and home environment were still present 20 years later in the most fragile individuals, and KMC parents were more protective and nurturing, reflected by reduced school absenteeism and reduced hyperactivity, aggressiveness, externalization, and socio-deviant conduct of young adults.** Neuroimaging showed larger volume of the left caudate nucleus in the KMC group.

### CONCLUSIONS:

This study indicates that KMC had significant, long-lasting social and behavioral protective effects 20 years after the intervention. Coverage with this efficient and scientifically based health care intervention should be extended to the 18 million infants born each year who are candidates for the method.

Free access: <http://pediatrics.aappublications.org/content/139/1/e20162063.long>

[Indian Pediatr.](#) 2017 Apr 15;54(4):279-283.

### **Comparative Efficacy and Safety of Caffeine and Aminophylline for Apnea of Prematurity in Preterm ( $\leq 34$ weeks) Neonates: A Randomized Controlled Trial.**

[Shivakumar M<sup>1</sup>](#), [Jayashree P](#), [Najih M](#), [Lewis LES](#), [Bhat Y R](#), [Kamath A](#), [Shashikala -](#).

#### **Abstract**

#### **OBJECTIVE:**

To compare the efficacy and safety of standard doses of Caffeine and Aminophylline for Apnea of prematurity.

#### **STUDY DESIGN:**

Randomized controlled trial.

#### **SETTING:**

Tertiary-care referral centre and a teaching institution in Southern India. Trial was conducted from February 2012 to January 2015.

#### **PARTICIPANTS:**

240 preterm ( $\leq 34$  wk) neonates with apnea of prematurity.

#### **INTERVENTIONS:**

Neonates randomized into two groups: **Caffeine group received loading dose of caffeine citrate (20 mg/kg) followed by 5 mg/kg/day maintenance dose every 24 hour.**

**Aminophylline group received loading dose of Aminophylline - 5 mg/kg and maintenance dose of 1.5 mg/kg 8-hourly.**

#### **OUTCOME MEASURES:**

Difference in apneic spells, associated respiratory morbidity, and acute adverse events were assessed. Association of efficacy with therapeutic drug levels was also evaluated.

#### **RESULTS:**

Infants on aminophylline experienced less apnea spells in 4-7 days of therapy ( $P=0.03$ ). Mean apnea rate and isolated desaturations were similar in 1-3, 4-7 and 8-14 days of therapy. No difference was noted in duration of Neonatal Intensive Care Unit stay and hospital stay. Mean heart rate was significantly high in Aminophylline group ( $P<0.001$ ). Risk of developing



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tachycardia was less (RR 0.30; 95% CI range 0.15 to 0.60;  $P < 0.001$ ) in Caffeine- over Aminophylline-treated infants.

### CONCLUSION:

Aminophylline is as effective as caffeine for prevention of apneic spells in preterm neonates; however, dosage optimization needs to be done to reduce toxicity.

Free access: <https://www.indianpediatrics.net/apr2017/279.pdf>

[Acta Med Iran.](#) 2016 Dec;54(12):788-792.

### A Comparison of Early Ibuprofen and Indomethacin Administration to Prevent Intraventricular Hemorrhage Among Preterm Infants.

[Kalani M](#)<sup>1</sup>, [Shariat M](#)<sup>2</sup>, [Khalesi N](#)<sup>3</sup>, [Farahani Z](#)<sup>4</sup>, [Ahmadi S](#)<sup>5</sup>.

#### Abstract

Intraventricular hemorrhage (IVH) is one of the common morbidities among preterm neonates. In the present study, we set out to evaluate the efficacy of two prophylactic modalities (ibuprofen and indomethacin prophylaxis) for prevention of IVH in our local setting. A prospective study was carried out in Akbar-Abadi Hospital, Tehran-Iran (2013-2014). Ninety-six preterm neonates who cared in closed incubator entered the study. Neonates randomly assigned into 3 groups; control, oral indomethacin (0.2 mg/kg indomethacin daily for 3 days) and oral ibuprofen (10,5,5 mg/kg ibuprofen every 24 hours during 3) administration. For all subjects brain sonography examination was performed in 3rd day, first, 2nd week of life and when infants reached to 36 and 42 weeks of postmenstrual age. The IVH prevalence and the effectiveness of the drugs among groups were statistically assessed. Of all 93 subjects; 14 cases had IVH (15.1%). IVH was significantly more frequent in the controls than in other groups ( $P = 0.049$ ). Prophylactic treatment could significantly decrease the incidence of grade 3 or 4 IVH in experimental groups ( $P = 0.008$ ). There were no significant differences between the three experimental groups with respect to the incidence of GI bleeding, Oliguria, renal dysfunction or NEC ( $P > 0.05$ ). This study demonstrates that low-dose prophylactic indomethacin and ibuprofen are equally associated with a reduction of IVH without any significant side effects like renal dysfunction, GI bleeding or NEC.

Free access: <http://acta.tums.ac.ir/index.php/acta/article/view/5774/4880>

#### Comment

*A Cochrane review of 19 trials involving 2872 infants concluded that prophylactic treatment with indomethacin has a number of immediate benefits, in particular a reduction in symptomatic patent ductus arteriosus, the need for duct ligation and severe intraventricular haemorrhage. In particular prophylactic indomethacin significantly reduces the incidence of Grade 3 and 4 intraventricular haemorrhage, pooled RR = 0.66 (0.53 to 0.82). However there is no evidence that prophylactic use of indomethacin has any effect on mortality in preterm babies, and carries a risk of oliguria. (<http://onlinelibrary.wiley.com/doi/10.1002/ebch.526/abstract>) The balance of whether indomethacin is beneficial or not in pre-term babies may depend on whether the baby has a PDA, if not then there is no mechanistic reason why indomethacin should prevent IVH, and the risk of reduced cerebral blood flow from indomethacin exists.*

[Paediatr Int Child Health.](#) 2016 Nov;36(4):288-295. Epub 2016 Jun 1.

### A randomised controlled trial of high vs low volume initiation and rapid vs slow advancement of milk feeds in infants with birthweights $\leq 1000$ g in a resource-limited setting.



[Raban S<sup>1</sup>](#), [Santhakumaran S<sup>2</sup>](#), [Keraan Q<sup>1</sup>](#), [Joolay Y<sup>1</sup>](#), [Uthaya S<sup>3</sup>](#), [Horn A<sup>1</sup>](#), [Modi N<sup>3</sup>](#), [Harrison M<sup>1</sup>](#).

**BACKGROUND:**

Optimal feeding regimens for infants  $\leq 1000$  g have not been established and are a global healthcare concern.

**AIMS AND OBJECTIVES:**

A controlled trial to establish the safety and efficacy of high vs low volume initiation and rapid vs slow advancement of milk feeds in a resource-limited setting was undertaken.

**METHODS:**

**Infants  $\leq 1000$  g birthweight were randomised to one of four arms, either low (4 ml/kg/day) or high (24 ml/kg/day) initiation and either slow (24 ml/kg/day) or rapid (36 ml/kg/day) advancement of exclusive feeds of human milk (mother's or donor) until a weight of 1200 g was reached.** After this point, formula was used to supplement insufficient mother's milk. The primary outcome was time to reach 1500 g.

**RESULTS:**

infants were recruited (51: low/slow; 47: low/rapid; 52: high/slow; 50: high/rapid). **Infants on rapid advancement regimens reached 1500 g most rapidly (hazard ratio 1.48, 95% CI 1.05-2.09,  $P=0.03$ ). The rapid advancement groups also regained birthweight more rapidly (hazard ratio 1.77, 95% CI 1.26-2.50,  $P=0.001$ ).** There was no apparent effect of high vs low initiation volumes but there was some evidence of interaction between interventions. There were no significant differences in other secondary outcomes, including necrotising enterocolitis, feed intolerance and late-onset sepsis.

**CONCLUSIONS:**

In this small pilot study, **higher initiation feed volumes and larger daily increments appeared to be well tolerated and resulted in more rapid early weight gain.** These data provide justification for a larger study in resource-limited settings to address mortality, necrotising enterocolitis and other important outcomes.

[J Pediatr Gastroenterol Nutr.](#) 2017 May;64(5):e126-e132. doi:

10.1097/MPG.0000000000001451.

**[Effect of Differential Enteral Protein on Growth and Neurodevelopment in Infants <1500 g: A Randomized Controlled Trial.](#)**

[Dogra S<sup>1</sup>](#), [Thakur A](#), [Garg P](#), [Kler N](#).

**OBJECTIVE:**

The aim of the study was to determine whether higher enteral protein intake leads to improved head growth at 40 weeks postmenstrual age (PMA) in preterm infants <32 weeks or 1500 g.

**METHODS:**

Randomized controlled trial in which **120 infants were assigned to either group A with higher enteral protein intake achieved by fortification with higher protein containing fortifier (1 g/100 mL expressed breast milk) or to group B with lower enteral protein intake where fortification was done with standard available protein fortifier (0.4 g /100 mL expressed breast milk).**

**RESULTS:**

The mean (standard deviation) protein intake was higher in group A as compared to group B; 4.2 (0.47) compared with 3.6 (0.37) g · kg · day,  $P<0.001$ . At 40 weeks PMA, the mean (standard deviation) weekly occipitofrontal circumference gain was significantly higher in group A as compared to group B; 0.66 (0.16) compared with 0.60 (0.15) cm/week (mean difference 0.064, 95% confidence interval [0.004-0.123], [ $P=0.04$ ]). Weight growth velocity in group A was 11.95 (2.2) g · kg · day as compared to 10.78 (2.6) g · kg · day in group B (mean difference 1.10,

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95% confidence interval [0.25-2.07], [P=0.01]). No difference was observed in the length between the 2 groups. There was no difference in growth indices and neurodevelopmental outcomes at 12 to 18 months corrected age in the 2 groups.

### CONCLUSIONS:

Fortification of expressed human milk with fortifier containing higher protein results in better head growth and weight gain at 40 weeks PMA in preterm infants <32 weeks or 1500 g without any benefits on long-term growth and neurodevelopment at 12 to 18 months corrected age

[J Perinatol](#). 2016 Sep;36(9):763-7. doi: 10.1038/jp.2016.70. Epub 2016 May 5.

### A randomized double-blind controlled trial comparing two regimens of vitamin D supplementation in preterm neonates.

[Tergestina M](#)<sup>1</sup>, [Rebekah G](#)<sup>2</sup>, [Job V](#)<sup>3</sup>, [Simon A](#)<sup>4</sup>, [Thomas N](#)<sup>1</sup>.

### OBJECTIVE:

To compare the efficacy of 400 vs 1000 IU oral vitamin D supplementation in preterm neonates of 27 to 34 weeks gestation.

### METHODS:

This double-blind randomized controlled trial allocated preterm babies to receive either 400 or 1000 IU of vitamin D3 (n=60 in each group). Primary outcome was prevalence of vitamin D insufficiency (serum vitamin D levels<20 ng ml(-1)) at 40 weeks of corrected gestational age (CGA).

### RESULTS:

At term CGA vitamin D insufficiency was significantly lower in the 1000 IU group than in the 400 IU group (2% vs 64.6%,  $P \leq 0.001$ ). Although elevated vitamin D levels were seen in 9.8% of babies on 1000 IU per day, this was not associated with clinical or biochemical evidence of toxicity.

### CONCLUSION:

**Supplementing preterm babies with 1000 IU of vitamin D3 daily decreases the prevalence of vitamin D insufficiency at term CGA.** Excess levels of vitamin D may occur at this dose in some babies.

## Neonatal infection

[BMC Pediatr](#). 2016 Aug 2;16:121. doi: 10.1186/s12887-016-0625-7.

### Effect of 4 % chlorhexidine on cord colonization among hospital and community births in India: a randomized controlled study.

[Nangia S](#)<sup>1</sup>, [Dhingra U](#)<sup>2,3</sup>, [Dhingra P](#)<sup>3,4</sup>, [Dutta A](#)<sup>3</sup>, [Menon VP](#)<sup>4</sup>, [Black RE](#)<sup>2</sup>, [Sazawal S](#)<sup>5,6,7</sup>.

### Author information

### BACKGROUND:

Infections are the single most important cause of neonatal mortality in developing countries. Results from trials in Asia evaluating the effect of chlorhexidine on neonatal mortality have been encouraging but limited data are available on the impact of cord cleansing on bacterial colonization. Further, no data from facility deliveries and impact with time is available. This pilot study was aimed to evaluate the impact of 4 % commercially prepared chlorhexidine on cord colonization and density of colonization among newborns in India.

### METHODS:

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Three hundred twenty-six newborns (hospital-247; community-79) were enrolled within 24 h of birth and randomly assigned to one of three groups: chlorhexidine, placebo or dry cord care. Umbilical swabs were collected at baseline, 2- and 48- hours after intervention application.

### RESULTS:

At baseline, growth positivity (any bacterial growth) was 20 % (50 of 247 swabs) and 81 % (64 of 79 swabs) among hospital and community born neonates, respectively. In both settings, chlorhexidine compared to placebo and dry cord care, reduced colonization following 2- and 48-hour post application. **Chlorhexidine significantly reduced 48-hour post application colony counts in comparison to placebo [Hospital: mean difference = -1.01; 95 % CI: -1.72, -0.30 Community: mean difference = -1.76; 95 % CI: -2.60, -0.93] and dry cord care [Hospital: mean difference = -1.16; 95 % CI: -1.93, -0.39 Community: mean difference = -2.23; 95 % CI: -3.18, -1.29].** Differences were similar for gram-positive and gram-negative bacteria.

### CONCLUSIONS:

Cord cleansing with 4 % chlorhexidine soon after birth reduced colonization as well as density of colonization significantly; however this pilot study does not address the impact of chlorhexidine on mortality. The control preparation neither increased or decreased colonization.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4971644/>

[World J Pediatr](#). 2016 Nov;12(4):408-414. Epub 2016 Feb 1.

### Feasibility and efficacy of gentamicin for treating neonatal sepsis in community-based settings: a systematic review.

[Jaiswal N<sup>1</sup>](#), [Singh M<sup>1,2</sup>](#), [Kondel R<sup>3</sup>](#), [Kaur N<sup>3</sup>](#), [Thumburu KK<sup>1</sup>](#), [Kumar A<sup>1</sup>](#), [Kaur H<sup>4</sup>](#), [Chadha N<sup>5</sup>](#), [Gupta N<sup>6</sup>](#), [Agarwal A<sup>1</sup>](#), [Malhotra S<sup>3</sup>](#), [Shafiq N<sup>7</sup>](#).

### BACKGROUND:

Neonatal sepsis is a leading cause of neonatal deaths in developing countries. The current recommended in-hospital treatment is parenteral ampicillin (or penicillin) and gentamicin in young infants for 10- 14 days; however, very few could access and afford. The current review is to evaluate the feasibility of gentamicin in community based settings.

### METHODS:

Both observational and randomized controlled trials were included. Medline, Embase, Cochrane Central Register of Controlled Trials and Central Trial Register of India were searched until September 2013. We assessed the risk of bias by Cochrane Collaboration's "risk of bias" tool.

### RESULTS:

Two observational studies indicated feasibility ensuring coverage of population, decrease in case fatality rate in the group treated by community health workers. In an RCT, no significant difference was observed in the treatment failure rates [odds ratio (OR)=0.88], and the mortality in the first and second week (OR=1.53; OR=2.24) between gentamicin and ceftriaxone groups. Within the gentamicin group, the combination of penicillin and gentamicin showed a lower rate of treatment failure (OR=0.44) and mortality at second week of life (OR=0.17) as compared to the combination of gentamicin and oral cotrimoxazole.

### CONCLUSION:

Gentamicin for the treatment of neonatal sepsis is both feasible and effective in community-based settings and can be used as an alternative to the hospital based care in resource compromised settings. But there was less evidence in the management of neonatal sepsis in hospitals as was seen in this review in which we included only one RCT and three observational studies.

## Nutrition, micronutrients and breast feeding

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

### Micronutrients, multivitamins and food fortification

(See also Vitamin A)

[Am J Clin Nutr.](#) 2017 Apr;105(4):958-969. doi: 10.3945/ajcn.116.150318. Epub 2017 Mar 8.

#### **Home fortification during the first 1000 d improves child development in Bangladesh: a cluster-randomized effectiveness trial.**

[Matias SL](#)<sup>1</sup>, [Mridha MK](#)<sup>2,3</sup>, [Tofail F](#)<sup>3,4</sup>, [Arnold CD](#)<sup>2</sup>, [Khan MS](#)<sup>5</sup>, [Siddiqui Z](#)<sup>3</sup>, [Ullah MB](#)<sup>2</sup>, [Dewey KG](#)<sup>2</sup>.

#### **Abstract**

Background: Nutrition during the first 1000 d is critical for brain development.

Objective: We evaluated the effects on child development of **home fortification with lipid-based nutrient supplements (LNSs) for mothers and/or children or micronutrient powder (MNP) for children.**

Design: We conducted a cluster-randomized effectiveness trial with 4 arms: 1) LNSs during pregnancy and the first 6 mo postpartum and LNSs for the offspring from 6 to 24 mo (LNS-LNS), 2) iron and folic acid (IFA) during pregnancy and the first 3 mo postpartum and LNSs for the children from 6 to 24 mo (IFA-LNS), 3) IFA (as above) and MNP for the offspring from 6 to 24 mo (IFA-MNP), and 4) IFA (as above) and no child supplement (IFA-Control). Women were enrolled at  $\leq 20$  wk of gestation; children were assessed at 12 (n = 3331), 18 (n = 3364), and 24 (n = 3379) mo.

Results: Compared with the IFA-Control group, motor development scores were higher in the LNS-LNS (P = 0.016) and IFA-LNS groups (P = 0.006) at 18 mo and in the IFA-MNP group (P = 0.048) at 24 mo. Receptive language scores were higher for the LNS-LNS group (P = 0.028) at 18 mo and for all 3 groups at 24 mo (P = 0.008 for LNS-LNS, P = 0.022 for IFA-LNS, and P = 0.009 for IFA-MNP compared with IFA-Control). Expressive language scores did not differ at 18 mo (P = 0.236) but were higher in the LNS-LNS (P = 0.035) and IFA-MNP (P = 0.002) groups than in the IFA-Control group at 24 mo. Groups did not differ in personal-social scores at 18 (P = 0.233) or 24 (P = 0.146) mo or in executive function score at 24 mo (P = 0.467).

Conclusion: **Prenatal LNSs, postnatal LNSs, or both, or postnatal MNP had a positive effect on motor and language development in Bangladeshi children.**

[Am J Clin Nutr.](#) 2017 Apr;105(4):944-957. doi: 10.3945/ajcn.116.147942. Epub 2017 Mar 8.

#### **Lipid-based nutrient supplementation in the first 1000 d improves child growth in Bangladesh: a cluster-randomized effectiveness trial.**

[Dewey KG](#)<sup>1</sup>, [Mridha MK](#)<sup>2,3</sup>, [Matias SL](#)<sup>2</sup>, [Arnold CD](#)<sup>2</sup>, [Cummins JR](#)<sup>4</sup>, [Khan MS](#)<sup>5</sup>, [Maalouf-Manasseh Z](#)<sup>6</sup>, [Siddiqui Z](#)<sup>3</sup>, [Ullah MB](#)<sup>2</sup>, [Vosti SA](#)<sup>7</sup>.

#### **Abstract**

Background: Stunting in linear growth occurs mainly during the first 1000 d, from conception through 24 mo of age. Despite the recognition of this critical period, there have been few evaluations of the growth impact of interventions that cover most of this window.

Objective: We evaluated home fortification approaches for preventing maternal and child undernutrition within a community-based health program. We hypothesized that small-quantity lipid-based nutrient supplements (LNSs) provided to women during pregnancy and the first 6

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mo postpartum, LNSs provided to their offspring from 6 to 24 mo of age, or both would result in greater child length-for-age z score (LAZ) at 24 mo than iron and folic acid (IFA) provided to women during pregnancy and postpartum plus micronutrient powder (MNP) or no supplementation for their offspring from 6 to 24 mo.

**Design:** We conducted a cluster-randomized effectiveness trial with 4 arms: 1) women and children both received LNSs (LNS-LNS group), 2) women received IFA and children received LNSs (IFA-LNS group), 3) women received IFA and children received MNP (IFA-MNP group), and 4) women received IFA and children received no supplements (IFA-Control group). We enrolled 4011 women at  $\leq 20$  wk of gestation within 64 clusters, each comprising the supervision area of a community health worker. Analyses were primarily performed by using ANCOVA F tests and Tukey-Kramer-corrected pairwise comparisons.

**Results:** At 24 mo, the LNS-LNS group had significantly higher LAZ (+0.13 compared with the IFA-MNP group) and head circumference (+0.15 z score compared with the IFA-Control group); these outcomes did not differ between the other groups. Stunting prevalence (LAZ  $< -2$ ) was lower in the LNS-LNS group at 18 mo than in the IFA-MNP group (OR: 0.70; 95% CI: 0.53, 0.92), but the difference diminished by 24 mo (OR: 0.81; 95% CI: 0.63, 1.04). **Conclusion:** Home fortification with small-quantity LNSs, but not MNP, during the first 1000 d improved child linear growth and head size in rural Bangladesh. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01715038) as [NCT01715038](https://clinicaltrials.gov/ct2/show/study/NCT01715038).

[Am J Clin Nutr.](#) 2016 Sep;104(3):797-808. doi: 10.3945/ajcn.116.134692. Epub 2016 Aug 17. **[Small-quantity, lipid-based nutrient supplements provided to women during pregnancy and 6 mo postpartum and to their infants from 6 mo of age increase the mean attained length of 18-mo-old children in semi-urban Ghana: a randomized controlled trial.](#)**

[Adu-Afarwuah S](#)<sup>1</sup>, [Lartey A](#)<sup>2</sup>, [Okronipa H](#)<sup>2</sup>, [Ashorn P](#)<sup>3</sup>, [Peerson JM](#)<sup>4</sup>, [Arimond M](#)<sup>4</sup>, [Ashorn U](#)<sup>3</sup>, [Zeilani M](#)<sup>5</sup>, [Vosti S](#)<sup>4</sup>, [Dewey KG](#)<sup>4</sup>.

### **BACKGROUND:**

Childhood stunting usually begins in utero and continues after birth; therefore, its reduction must involve actions across different stages of early life.

### **OBJECTIVE:**

We evaluated the efficacy of small-quantity, lipid-based nutrient supplements (SQ-LNSs) provided during pregnancy, lactation, and infancy on attained size by 18 mo of age.

### **DESIGN:**

In this partially double-blind, individually randomized trial, 1320 women at  $\leq 20$  wk of gestation received standard iron and folic acid (IFA group), multiple micronutrients (MMN group), or SQ-LNS (LNS group) daily until delivery, and then placebo, MMNs, or SQ-LNS, respectively, for 6 mo postpartum; infants in the LNS group received SQ-LNS formulated for infants from 6 to 18 mo of age (endline). The primary outcome was child length by 18 mo of age.

### **RESULTS:**

At endline, data were available for 85% of 1228 infants enrolled; overall mean length and length-for-age z score (LAZ) were 79.3 cm and -0.83, respectively, and 12% of the children were stunted (LAZ  $< -2$ ). In analysis based on the intended treatment, mean  $\pm$  SD length and LAZ for the LNS group ( $79.7 \pm 2.9$  cm and  $-0.69 \pm 1.01$ , respectively) were significantly greater than for the IFA ( $79.1 \pm 2.9$  cm and  $-0.87 \pm 0.99$ ) and MMN ( $79.1 \pm 2.9$  cm and  $-0.91 \pm 1.01$ ) groups ( $P = 0.006$  and  $P = 0.009$ , respectively). Differences were also significant for weight and weight-for-age z score but not head or midupper arm circumference, and the prevalence of stunting in the LNS group was 8.9%, compared with 13.7% in the IFA group and 12.9% in the MMN group ( $P = 0.12$ ). In analysis based on actual supplement provided at enrollment, stunting prevalences were 8.9% compared with 15.1% and 11.5%, respectively ( $P = 0.045$ ).



**CONCLUSION:**

Provision of SQ-LNSs to women from pregnancy to 6 mo postpartum and to their infants from 6 to 18 mo of age may increase the child's attained length by age 18 mo in similar settings.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4997301/>

[Br J Nutr.](#) 2017 Feb;117(4):511-518. doi: 10.1017/S0007114517000290.

**Effect of 12-month intervention with lipid-based nutrient supplement on the physical activity of Malawian toddlers: a randomised, controlled trial.**

[Pulakka A](#)<sup>1</sup>, [Cheung YB](#)<sup>2</sup>, [Maleta K](#)<sup>3</sup>, [Dewey KG](#)<sup>4</sup>, [Kumwenda C](#)<sup>5</sup>, [Bendabenda J](#)<sup>3</sup>, [Ashorn U](#)<sup>6</sup>, [Ashorn P](#)<sup>6</sup>.

**Abstract**

Physical activity is beneficial for children's well-being. The effect of dietary supplementation on children's physical activity in food-insecure areas remains little studied. **We examined the effects of a lipid-based nutrient supplement (LNS) on children's objectively measured physical activity** in a randomised, controlled, outcome-assessor-blinded trial. Mothers of the children received one capsule daily of Fe-folic acid (IFA), one capsule containing eighteen micronutrients (MMN) or one 20 g sachet of LNS (containing twenty-two MMN, protein, carbohydrates, essential fatty acids and 494 kJ (118 kcal)) during pregnancy and for 6 months thereafter. Children in the IFA and MMN groups received no supplementation, and these groups were collapsed into a single control group; children in the LNS group received 20 g LNS from 6 to 18 months. We measured physical activity with accelerometers over 1 week at 18 months.

**The main outcome was mean vector magnitude counts/15 s.** Of the 728 children at the beginning of child intervention at 6 months, 570 (78 %) provided sufficient data for analysis. The mean accelerometer counts for the 190 children in the LNS group and for the 380 children in the control group were 303 (sd 59) and 301 (sd 56), respectively (P for difference=0.65). LNS, given to mothers during pregnancy and 6 months postpartum and to their infants from 6 to 18 months of age, did not increase physical activity among 18-month-old children.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5426340/>

[J Pediatr.](#) 2017 Feb;181:242-247.e2. doi: 10.1016/j.jpeds.2016.10.066. Epub 2016 Dec 7.

**Household Consumption of Thiamin-Fortified Fish Sauce Increases Erythrocyte Thiamin Concentrations among Rural Cambodian Women and Their Children Younger Than 5 Years of Age: A Randomized Controlled Efficacy Trial.**

[Whitfield KC](#)<sup>1</sup>, [Karakochuk CD](#)<sup>2</sup>, [Kroeun H](#)<sup>3</sup>, [Sokhoing L](#)<sup>3</sup>, [Chan BB](#)<sup>2</sup>, [Borath M](#)<sup>4</sup>, [Sophonneary P](#)<sup>5</sup>, [Moore K](#)<sup>2</sup>, [Tong JK](#)<sup>2</sup>, [McLean J](#)<sup>2</sup>, [Talukder A](#)<sup>3</sup>, [Lynd LD](#)<sup>6</sup>, [Li-Chan EC](#)<sup>2</sup>, [Kitts DD](#)<sup>2</sup>, [Green TJ](#)<sup>7</sup>.

**OBJECTIVES:**

To assess whether ad libitum consumption of thiamin-fortified fish sauce over 6 months yields higher erythrocyte thiamin diphosphate concentrations (eTDP) among women of childbearing age and their children aged 12-59 months compared with control sauce containing no thiamin.

**STUDY DESIGN:**

In this double-blind, randomized controlled efficacy trial, 276 nonpregnant, nonlactating women (18-45 years of age) and their families in Prey Veng, Cambodia, were randomized to receive 1 of 3 fish sauce formulations: low thiamin concentration (low, 2 g/L), high thiamin concentration



(high, 8 g/L), or a control (no thiamin) fish sauce. Baseline (t = 0) and endline (t = 6 months) eTDP were measured with the use of high-performance liquid chromatography with a fluorescence detector.

**RESULTS:**

Fish sauce consumption did not differ between treatment groups ( $P = .19$ ). In intent-to-treat analysis, women's baseline-adjusted endline eTDP (mean; 95% CI) was higher among women in the low (259; 245-274 nmol/L) and high (257; 237-276 nmol/L) groups compared with control (184; 169-198 nmol/L;  $P < .001$ ); low and high groups did not differ ( $P = .83$ ). Similarly, children's baseline-adjusted eTDP was higher in the low (259; 246-271 nmol/L) and high (257; 243-270 nmol/L) groups compared with control (213; 202-224 nmol/L;  $P < .001$ ).

**CONCLUSION:**

**Fortified fish sauce appears to be an efficacious means of improving biochemical thiamin status in nonpregnant, nonlactating women and their children (1-5 years of age) living in rural Cambodia.**

[JAMA Pediatr.](#) 2016 Oct 3;170(10):e162065. doi: 10.1001/jamapediatrics.2016.2065. Epub 2016 Oct 3.

**Perinatal Consumption of Thiamine-Fortified Fish Sauce in Rural Cambodia: A Randomized Clinical Trial.**

[Whitfield KC](#)<sup>1</sup>, [Karakochuk CD](#)<sup>2</sup>, [Kroeun H](#)<sup>3</sup>, [Hampel D](#)<sup>4</sup>, [Sokhoing L](#)<sup>3</sup>, [Chan BB](#)<sup>2</sup>, [Borath M](#)<sup>5</sup>, [Sophonneary P](#)<sup>6</sup>, [McLean J](#)<sup>2</sup>, [Talukder A](#)<sup>3</sup>, [Lynd LD](#)<sup>7</sup>, [Li-Chan EC](#)<sup>2</sup>, [Kitts DD](#)<sup>2</sup>, [Allen LH](#)<sup>4</sup>, [Green TJ](#)<sup>8</sup>.

**Importance:**

Infantile beriberi, a potentially fatal disease caused by thiamine deficiency, remains a public health concern in Cambodia and regions where thiamine-poor white rice is a staple food. Low maternal thiamine intake reduces breast milk thiamine concentrations, placing breastfed infants at risk of beriberi.

**Objective:**

To determine if consumption of thiamine-fortified fish sauce yields higher erythrocyte thiamine diphosphate concentrations (eTDP) among lactating women and newborn infants and higher breast milk thiamine concentrations compared with a control sauce.

**Design, Setting, and Participants:**

In this double-blind randomized clinical trial, 90 pregnant women were recruited in the Prey Veng province, Cambodia. The study took place between October 2014 and April 2015.

**Interventions:**

Women were randomized to 1 of 3 groups (n = 30) for ad libitum fish sauce consumption for 6 months: control (no thiamine), low-concentration (2 g/L), or high-concentration (8 g/L) fish sauce.

**Main Outcomes and Measures:**

Maternal eTDP was assessed at baseline (October 2014) and endline (April 2015). Secondary outcomes, breast milk thiamine concentration and infant eTDP, were measured at endline.

**Results:**

Women's mean (SD) age and gestational stage were 26 (5) years and 23 (7) weeks, respectively. April 2015 eTDP was measured among 28 women (93%), 29 women (97%), and 23 women (77%) in the control, low-concentration, and high-concentration groups, respectively. In modified intent-to-treat analysis, mean baseline-adjusted endline eTDP was higher among women in the low-concentration (282nM; 95% CI, 235nM to 310nM) and high-concentration (254nM; 95% CI, 225nM to 284nM) groups compared with the control group (193nM; 95% CI, 164nM to 222M;  $P < .05$ ); low-concentration and high-concentration groups did not differ

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( $P = .19$ ). Breast milk total thiamine concentrations were 14.4  $\mu\text{g/dL}$  for the control group (95% CI, 12.3  $\mu\text{g/dL}$  to 16.5  $\mu\text{g/dL}$ ) (to convert to nanomoles per liter, multiply by 29.6); 20.7  $\mu\text{g/dL}$  for the low-concentration group (95% CI, 18.6  $\mu\text{g/dL}$  to 22.7  $\mu\text{g/dL}$ ); and 17.7  $\mu\text{g/dL}$  for the high-concentration group (95% CI, 15.6  $\mu\text{g/dL}$  to 19.9  $\mu\text{g/dL}$ ). Mean (SD) infant age at endline was 16 (8) weeks for the control group, 17 (7) weeks for the low-concentration group, and 14 (8) for the high-concentration group. Infant eTDP was higher among those in the high-concentration group (257nM; 95% CI, 222nM to 291nM;  $P < .05$ ) compared with the low-concentration (212nM; 95% CI, 181nM to 244nM) and control (187nM; 95% CI, 155nM to 218nM) groups.

### Conclusions and Relevance:

**Compared with women in the control group, women who consumed thiamine-fortified fish sauce through pregnancy and early lactation had higher eTDP and breast milk thiamine concentrations and their infants had higher eTDP, which was more pronounced in the high group.** Thiamine-fortified fish sauce has the potential to prevent infantile beriberi in this population.

### Comment

*The above 2 studies by the same authors, of thiamine-fortified fish sauce have the same methodology. The difference is that one was in pregnant women and their children, and one in women who were not pregnant, and their children. The direction of the results is the same.*

[Pediatr Int.](#) 2016 Nov;58(11):1193-1199. doi: 10.1111/ped.13011. Epub 2016 Aug 31.

[Effect of zinc plus multivitamin supplementation on growth in school children.](#)

[Rerksuppaphol S](#)<sup>1</sup>, [Rerksuppaphol L](#)<sup>2</sup>.

### BACKGROUND:

Zinc and multiple vitamins are essential for growth. Zinc and vitamin deficiency is very common in developing countries. The aim of this study was to assess the efficacy of zinc plus multivitamin supplements in improving growth of healthy Thai schoolchildren.

### METHODS:

A randomized controlled trial was conducted in healthy 4-13-year-old Thai schoolchildren attending public school in central Thailand. Participants were **randomized to receive either chelated zinc in the form of zinc bis-glycinate (20 mg elemental zinc) plus multivitamins (vitamin A, 1000 IU; vitamin D, 200 IU; B1, 10 mg; B2, 3 mg; B6, 1 mg; B12, 10  $\mu\text{g}$ ; nicotinamide, 40 mg) or placebo once per day, 5 days per week for 6 months.** Primary outcome was change in height from baseline to the end of the study. Secondary outcomes were change in weight, body mass index, waist and hip circumferences and waist-to-height ratio. An intention-to-treat analysis was performed.

### RESULTS:

Seventy children each were randomized to the treatment and placebo groups. **The children who received zinc and multivitamins had significantly higher gain in height ( $4.9 \pm 1.3$  vs  $3.6 \pm 0.9$  cm, respectively;  $P < 0.001$ ).** Subgroup analysis showed significant improvement in height, especially in preadolescents. The increased gain in height was irrespective of baseline height and weight. The extra gain in height occurred after 2 months of supplementation. The changes in other anthropometric indices were not significantly different.

### CONCLUSION:

Supplementation of chelated zinc plus multivitamins for 6 months significantly increased height gain in Thai schoolchildren and was well tolerated.

[Am J Clin Nutr.](#) 2016 Nov;104(5):1318-1326. Epub 2016 Oct 12.

**Effects of wheat-flour biscuits fortified with iron and EDTA, alone and in combination, on blood lead concentration, iron status, and cognition in children: a double-blind randomized controlled trial.**

[Bouhouch RR](#)<sup>1</sup>, [El-Fadeli S](#)<sup>2</sup>, [Andersson M](#)<sup>1</sup>, [Aboussad A](#)<sup>3</sup>, [Chabaa L](#)<sup>3</sup>, [Zeder C](#)<sup>1</sup>, [Kippler M](#)<sup>4</sup>, [Baumgartner J](#)<sup>5</sup>, [Sedki A](#)<sup>2</sup>, [Zimmermann MB](#)<sup>6</sup>.

**Abstract**

**BACKGROUND:**

Lead is a common neurotoxicant and its absorption may be increased in iron deficiency (ID). Thus, iron fortification to prevent ID in populations is a promising lead mitigation strategy. Two common fortificants are ferrous sulfate (FeSO<sub>4</sub>) and ferric sodium EDTA (NaFeEDTA). EDTA can chelate iron and lead.

**OBJECTIVES:**

Our study objective was to determine the effects of iron and EDTA, alone and in combination, on blood lead (BPb) concentration, iron status, and cognition.

**DESIGN:**

In this 2 × 2 factorial, double-blind placebo-controlled trial, 457 lead-exposed Moroccan children were stratified by school and grade and randomly assigned to consume biscuits (6 d/wk at school) containing 1) ~ 8 mg Fe as FeSO<sub>4</sub>, 2) ~ 8 mg Fe as NaFeEDTA that contained ~ 41 mg EDTA, 3) ~ 41 mg EDTA as sodium EDTA (Na<sub>2</sub>EDTA), or 4) placebo for 28 wk. The primary outcome was BPb concentration; secondary outcomes were iron status and cognitive outcomes from subtests of the Kaufman Assessment Battery for Children and the Hopkins Verbal Learning Test. These outcomes were measured at baseline and endpoint. All data were analyzed by intention-to-treat.

**RESULTS:**

The adjusted geometric mean BPb concentration at baseline was 4.3 µg/dL (95% CI: 4.2, 4.3 µg/dL), and at endpoint these values were 3.3 µg/dL (95% CI: 3.1, 3.5 µg/dL) for FeSO<sub>4</sub>, 2.9 µg/dL (95% CI: 2.7, 3.0 µg/dL) for NaFeEDTA, 3.3 µg/dL (95% CI: 3.1, 3.5 µg/dL) for EDTA, and 3.7 µg/dL (95% CI: 3.5, 3.9 µg/dL) for placebo. We found an effect of iron (P = 0.009) and EDTA (P = 0.012) for reduced BPb concentrations at endpoint, but no iron × EDTA interaction. Iron fortification improved iron status, but there were no positive effects of iron or EDTA on cognitive test scores.

**CONCLUSIONS:**

**Food fortification with iron and EDTA additively reduces BPb concentrations.** Our findings suggest that NaFeEDTA should be the iron fortificant of choice in lead-exposed populations.

[J Nutr.](#) 2016 Oct;146(10):2093-2101. Epub 2016 Aug 31.

**Micronutrient Adequacy and Dietary Diversity Exert Positive and Distinct Effects on Linear Growth in Urban Zambian Infants.**

[Mallard SR](#)<sup>1</sup>, [Houghton LA](#)<sup>2</sup>, [Filteau S](#)<sup>3</sup>, [Chisenga M](#)<sup>4</sup>, [Siame J](#)<sup>4</sup>, [Kasonka L](#)<sup>4</sup>, [Mullen A](#)<sup>3</sup>, [Gibson RS](#)<sup>2</sup>.

**BACKGROUND:**

In the monitoring of infant and young child feeding, dietary diversity is used as an indicator of micronutrient adequacy; however, their relation may have weakened with the increasing use of fortified complementary foods.

### OBJECTIVE:

The objectives were to assess the relation between dietary diversity and micronutrient adequacy in an urban infant population with a high consumption of fortified foods and to investigate whether dietary diversity and micronutrient adequacy were independently associated with subsequent growth.

### METHODS:

We used longitudinal data on 811 infants in the Chilenje Infant Growth, Nutrition, and Infection Study conducted in Lusaka, Zambia. **The relation between mean micronutrient adequacies and dietary diversity scores derived from 24-h diet recalls at 6 mo of age was investigated** with the use of Spearman rank correlation. Multiple linear regression was used to assess the association between micronutrient adequacy, dietary diversity, and subsequent growth to 18 mo of age.

### RESULTS:

Overall mean micronutrient density adequacy (MMDA) and MMDA of "problem micronutrients," defined as those micronutrients (calcium, iron, zinc) with mean density adequacies less than half of estimated needs, were correlated with dietary diversity scores ( $\rho = 0.36$  and  $0.30$ , respectively, both  $P < 0.0001$ ). Consumption of "sentinel foods" (iron rich, fortified, animal source, dairy) showed better correlation with MMDA than with dietary diversity ( $\rho = 0.58$ - $0.69$ , all  $P < 0.0001$ ). **In fully adjusted analyses, MMDA calcium, iron, zinc, and dietary diversity, but not overall MMDA, were associated with linear growth to 18 mo (both  $P \leq 0.028$ ).**

### CONCLUSIONS:

Micronutrient adequacy in infants consuming fortified foods may be more accurately assessed using locally specific sentinel food indicators rather than dietary diversity scores. Nonetheless, dietary diversity has a positive effect on subsequent linear growth apart from that of micronutrient adequacy, warranting its continued monitoring and further investigation into the mechanisms underlying this finding.

## Environmental enteric dysfunction

[J Nutr.](#) 2017 Jan;147(1):97-103. doi: 10.3945/jn.116.237735. Epub 2016 Nov 2.

### **A Combined Intervention of Zinc, Multiple Micronutrients, and Albendazole Does Not Ameliorate Environmental Enteric Dysfunction or Stunting in Rural Malawian Children in a Double-Blind Randomized Controlled Trial.**

[Wang AZ](#)<sup>1,2</sup>, [Shulman RJ](#)<sup>3,4</sup>, [Crocker AH](#)<sup>2</sup>, [Thakwalakwa C](#)<sup>5</sup>, [Maleta KM](#)<sup>5</sup>, [Devaraj S](#)<sup>6</sup>, [Manary MJ](#)<sup>7,3,5</sup>, [Trehan I](#)<sup>7,8</sup>.

### BACKGROUND:

Environmental enteric dysfunction (EED) and linear growth stunting affect many rural agrarian children in the developing world and contribute to the persistently high rates of stunting that are observed worldwide. Effective interventions to consistently ameliorate EED are lacking.

### OBJECTIVE:

We tested whether a bundle of safe and affordable interventions would decrease EED and stunting over 12-24 wk in a cohort of rural Malawian children 12-35 mo old.

### METHODS:

This was a **randomized, double-blind, placebo-controlled clinical trial in which the intervention group received a single dose of albendazole and 14 d of zinc at enrollment and after 20 wk. The intervention group also received a daily multiple micronutrient powder throughout the 24 wk of study.** The primary outcomes were improvements in EED, as

measured by the **urinary lactulose-to-mannitol ratio (L:M ratio) from dual-sugar absorption testing, and linear growth**. Urinary L:M ratios and anthropometric measurements were evaluated **after 12 and 24 wk of intervention and compared with a placebo group that did not receive any of these interventions**.

### RESULTS:

A total of 254 children were enrolled at a mean age of 24 mo; 55% were female. Their mean weight-for-age z score was -1.5, and their mean length-for-age z score was -0.9. **After 12 and 24 wk of study, increases in the L:M ratio did not differ between the intervention group (0.071 and 0.088 units, respectively) and the placebo group (0.073 and 0.080 units, respectively) (P = 0.87 and 0.19, respectively)**. Relative changes in length and weight also did not differ significantly between groups at any time point.

### CONCLUSION:

**The combined usage of albendazole, zinc, and a daily multiple micronutrient powder did not decrease EED or stunting in this population of agrarian children 12-35 mo old in rural Malawi**. Alternative interventions to improve these diseases should be investigated.

### Comment

*This is an important paper on an important subject that is under-recognised, affecting children living in the poorest of circumstances. Environmental enteropathy is a chronic inflammatory state of the duodenum and jejunum, associated with mucosal villus atrophy, crypt hyperplasia and inflammatory cell infiltrate (CD8+ T-cell lymphocytes). The villi are broad and flat with increases in the crypt depth between villi. The surface area available for nutrient absorption is markedly reduced. There is moderate malabsorption, often subclinical, often without diarrhoea. Absorption of essential fats, carbohydrates and vitamins is decreased. Because it is an indolent chronic condition it leads to stunting. Environmental enteropathy is likely to be caused by faecal bacteria ingested in large quantities by young children living in conditions of poor sanitation and hygiene. The **lactulose: mannitol ratio**, as used in this study is believed to be a measure of environmental enteropathy. Lactulose is normally absorbed by the small intestine. Mannitol is a large molecule and normally not absorbed. Normally if a person ingests a given amount of a lactulose and mannitol, the amount of lactulose in the stool will be low (because it is absorbed) and the amount of mannitol in the stool will be high (because almost none of it is absorbed). In environmental enteropathy the lactulose: mannitol ratio in the stool is increased. The villous atrophy leads to reduced lactulose absorption (therefore more lost in the stool) and the intestinal hyper-permeability leads to translocation of the large molecule mannitol into the circulation (so less is excreted). Because of increased mucosal and sub-mucosal permeability there is bacterial and toxin translocation: lipopolysaccharide (the protein found on cell walls of enteric Gram negative bacteria), microbes and other toxins leak into the circulation from the gut lumen. This leads to chronic inflammation and sepsis-like conditions. The above trial confirms that multiple micronutrients and zinc alone have limited effect. Other interventions which may work include WASH: water, sanitation and hygiene. Toilets, handwashing, soap and running water, improved drinking water, exclusive breast feeding, properly prepared complementary feeding, and avoidance of bottle feeding. Growth monitoring of children linked to local household environmental improvements, rather than growth monitoring just being linked to attempts to providing more calories for children who are failing to thrive. More research is needed into this condition.*

## Macronutrient nutrition and complementary feeding

(See also Vitamin A)

[J Nutr.](#) 2017 Apr;147(4):670-679. doi: 10.3945/jn.116.243907. Epub 2017 Feb 8.

**Social Franchising and a Nationwide Mass Media Campaign Increased the Prevalence of Adequate Complementary Feeding in Vietnam: A Cluster-Randomized Program Evaluation.**

[Rawat R](#)<sup>1</sup>, [Nguyen PH](#)<sup>2</sup>, [Tran LM](#)<sup>3</sup>, [Hajeebhoy N](#)<sup>3</sup>, [Nguyen HV](#)<sup>4</sup>, [Baker J](#)<sup>3</sup>, [Frongillo EA](#)<sup>5</sup>, [Ruel MT](#)<sup>1</sup>, [Menon P](#)<sup>1</sup>.

**Abstract**

Background: Rigorous evaluations of health system-based interventions in large-scale programs to improve complementary feeding (CF) practices are limited. **Alive & Thrive applied principles of social franchising within the government health system in Vietnam to improve the quality of interpersonal counseling (IPC) for infant and young child feeding combined with a national mass media (MM) campaign and community mobilization (CM).** Objective: We evaluated the impact of enhanced IPC + MM + CM (intensive) compared with standard IPC + less-intensive MM and CM (nonintensive) on CF practices and anthropometric indicators. Methods: A cluster-randomized, nonblinded evaluation design with cross-sectional surveys (n = ~ 500 children aged 6-23.9 mo and ~ 1000 children aged 24-59.9 mo/group) implemented at baseline (2010) and endline (2014) was used. Difference-in-difference estimates (DDEs) of impact were calculated for intent-to-treat (ITT) analyses and modified per-protocol analyses (MPAs; mothers who attended the social franchising at least once: 62%). Results: Groups were similar at baseline. **In ITT analyses, there were no significant differences between groups in changes in CF practices over time.** In the MPAs, greater improvements in the intensive than in the nonintensive group were seen for minimum dietary diversity [DDE: 6.4 percentage points (pps); P < 0.05] and minimum acceptable diet (8.0 pps; P < 0.05). Significant stunting declines occurred in both intensive (7.1 pps) and nonintensive (5.4 pps) groups among children aged 24-59.9 mo, with no differential decline. Conclusions: When combined with MM and CM, an at-scale social franchising approach to improve IPC, delivered through the existing health care system, significantly improved CF practices, but not child growth, among mothers who used counseling services at least once. A greater impact may be achieved with strategies designed to increase service utilization

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5368587/>

[Am J Clin Nutr.](#) 2016 Nov;104(5):1450-1458. Epub 2016 Sep 28.

**Effect of complementary food supplementation on breastfeeding and home diet in rural Bangladeshi children.**

[Campbell RK](#)<sup>1</sup>, [Hurley KM](#)<sup>1</sup>, [Shamim AA](#)<sup>2</sup>, [Shaikh S](#)<sup>1</sup>, [Chowdhury ZT](#)<sup>1</sup>, [Mehra S](#)<sup>1</sup>, [de Pee S](#)<sup>3</sup>, [Ahmed T](#)<sup>4</sup>, [West KP Jr](#)<sup>1</sup>, [Christian P](#)<sup>5</sup>.

**BACKGROUND:**

Complementary food supplements (CFSs) can enhance growth where stunting is common, but substitution for the usual diet may reduce observed benefits.

**OBJECTIVE:**

We aimed to characterize dietary diversity from home foods in a CFS efficacy trial and determine whether supplementation reduced breastfeeding frequency or displaced home foods.

**DESIGN:**

**In a cluster-randomized controlled trial in rural Bangladesh, children (n = 5499) received, for 1 y starting at age 6 mo, periodic child feeding counseling for mothers (control) or counseling plus 1 of 4 CFSs fed as a daily snack.** Breastfeeding status and past 24-h diet were assessed at enrollment and every 3 mo thereafter until 18 mo of age. A 7-food group dietary



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diversity score (DDS) was calculated from home foods only, and a DDS  $\geq 4$  constituted minimum dietary diversity (MDD).

### RESULTS:

#### **Most children (97%) were breastfed through 18 mo of age, and 24-h breastfeeding frequency did not differ by supplementation group.**

Child dietary diversity was low; only 51% of children met the MDD by 18 mo. Rice, potatoes, and biscuits (cookies) were the most frequently consumed foods, whereas the legumes, dairy, eggs, and vitamin A-rich fruit and vegetable food groups were each consumed by <50% of children. The odds of meeting the MDD through the consumption of home foods were equal or greater in the supplemented groups compared with the control group at all ages. High socioeconomic status and any maternal education were associated with increased odds of MDD at age 18 mo, whereas child sex and household food security were not associated with MDD.

### CONCLUSIONS:

In a setting where daily complementary food supplementation improved linear growth, there was no evidence that supplementation displaced breastfeeding or home foods, and the supplementation may have improved dietary diversity. Pathways by which supplementation with fortified foods may enhance dietary diversity, such as an improved appetite and increased body size, need elucidation.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5081719/>

### Comment

*Measuring and improving dietary diversity and the quality of complementary feeding is the subject of several controlled trials this year. This is a very positive development, as in previous years the research conducted has strongly favoured micronutrient trials. Growth faltering often occurs from 4 months of age, when mothers' milk supply is less, and where there is inadequate complementary feeding and lack of dietary diversity. Proving how to address this problem may or may not come from controlled trials, but often depends on education, financial resources, opportunity, status of women and mothers, maternal mental and physical health, family and community support, and a contribution of health services through growth monitoring, identifying mothers and children most at risk, education on dietary diversity, and nutritional supplementation.*

[Rev Saude Publica](#). 2016 Dec 22;50:83. doi: 10.1590/S1518-8787.2016050006622.

#### **Adherence to dietary recommendations for preschoolers: clinical trial with teenage mothers.**

[Soldateli B](#)<sup>1</sup>, [Vigo A](#)<sup>2</sup>, [Giugliani ER](#)<sup>3</sup>.

### OBJECTIVE:

To assess the effect of educational dietary intervention offered in the child's first year of life, as well as teenage mothers and grandmothers in carrying out the dietary recommendations at four to seven years.

### METHODS:

Randomized clinical trial initiated in 2006, in Porto Alegre, RS, involving 323 teenage mothers and grandmothers who cohabited. The intervention consisted of six counseling sessions on breastfeeding and healthy complementary feeding. The first session occurred in the maternity ward and the other ones in the households of mothers at seven, 15, 30, 60, and 120 days of the child's life. The information about the child's diet were obtained on a monthly basis in the first six months, every two months in the second half-year, and at four to seven years, using a food

frequency questionnaire. **To assess the adequacy of food consumption to the recommendations from the Ministry of Health, we elaborated a score system that would reflect the compliance with the Ten Steps for Healthy Toddlers from 2 to 10 Years.** The average scores of intervention and control groups were compared using the t-test.

### RESULTS:

**Low adherence to recommendations on child nutrition was found in the study population, with no difference in implementation the steps between the groups.** The score on the compliance with the steps was similar in both groups (9.6 [SD = 1.63] and 9.3 [SD = 1.60] in the intervention and control groups, respectively) and no influence of the cohabitation with the grandmother was found.

### CONCLUSIONS:

Educational dietary intervention in the first four months of the child's life for teenage mothers and grandmothers had no effect on the compliance with the recommendations at four to seven years of the child's life.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167099/>

## Breastfeeding

*J Nutr.* 2017 Feb;147(2):248-255. doi: 10.3945/jn.116.241737. Epub 2016 Dec 21.

### Following the World Health Organization's Recommendation of Exclusive Breastfeeding to 6 Months of Age Does Not Impact the Growth of Rural Gambian Infants.

Eriksen KG<sup>1</sup>, Johnson W<sup>2</sup>, Sonko B<sup>3</sup>, Prentice AM<sup>3,4</sup>, Darboe MK<sup>3</sup>, Moore SE<sup>3,5</sup>.

### BACKGROUND:

The WHO recommends exclusive breastfeeding (EBF) for the first 6 mo of life.

### OBJECTIVE:

The objective of this study was to assess the benefit of EBF to age 6 mo on growth in a large sample of rural Gambian infants at high risk of undernutrition.

### METHODS:

Infants with growth monitoring from birth to 2 y of age (n = 756) from the ENID (Early Nutrition and Immune Development) trial were categorized as exclusively breastfed if only breast milk and no other liquids or foods were given. EBF status was entered into confounder-adjusted multilevel models to test associations with growth trajectories by using >11,000 weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) z score observations.

### RESULTS:

Thirty-two percent of infants were exclusively breastfed to age 6 mo. **The mean age of discontinuation of EBF was 5.2 mo, and growth faltering started at ~ 3.5 mo of age.** Some evidence for a difference in WAZ and WHZ was found between infants who were exclusively breastfed to age 6 mo (EBF-6) and those who were not (nEBF-6), at 6 and 12 mo of age, with EBF-6 children having a higher mean z score. The differences in z scores between the 2 groups were small in magnitude (at 6 mo of age: 0.147 WAZ; 95% CI: -0.001, 0.293 WAZ; 0.189 WHZ; 95% CI: 0.038, 0.341 WHZ). No evidence for a difference between EBF-6 and nEBF-6 infants was observed for LAZ at any time point (6, 12, and 24 mo of age). Furthermore, a higher mean WLZ at 3 mo of age was associated with a subsequent higher mean age at discontinuation of EBF, which implied reverse causality in this setting (coefficient: 0.060; 95% CI: 0.008, 0.120).

### CONCLUSION:

**This study suggests that EBF to age 6 mo has limited benefit to the growth of rural Gambian infants**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5265696/>

[Int Breastfeed J](#). 2016 Dec 8;11:31. eCollection 2016.

**Early newborn ritual foods correlate with delayed breastfeeding initiation in rural Bangladesh.**

[Sundaram ME](#)<sup>1</sup>, [Ali H](#)<sup>2</sup>, [Mehra S](#)<sup>3</sup>, [Shamim AA](#)<sup>4</sup>, [Ullah B](#)<sup>5</sup>, [Rashid M](#)<sup>2</sup>, [Shaikh S](#)<sup>2</sup>, [Christian P](#)<sup>3</sup>, [Klemm RD](#)<sup>3</sup>, [West KP Jr](#)<sup>3</sup>, [Labrique A](#)<sup>3</sup>.

**Abstract**

**BACKGROUND:**

Early and exclusive breastfeeding may improve neonatal survival in low resource settings, but suboptimal breastfeeding still exists in areas with high infant mortality. **Prelacteal feeding, the practice of giving a non-breastmilk food as a neonate's first food, has been associated with suboptimal breastfeeding practices. We examined the association of feeding a non-breastmilk food in the first three days of life (early neonatal food, or ENF) with time from birth to initiation of breastfeeding among 25,286 Bangladeshi mother-neonate pairs, in a secondary analysis of a randomized controlled trial in northwestern rural Bangladesh conducted from 2001-2007.**

**METHODS:**

Trained interviewers assessed the demographic characteristics during pregnancy. At three months postpartum, the interviewers visited participants again and retrospectively assessed demographic and breastfeeding characteristics surrounding the birth. We assessed the relationship between ENF and time to initiation of breastfeeding in hours in both unadjusted and adjusted linear regression analyses. We also calculated reverse cumulative distribution curves for time to initiation of breastfeeding and analyses were stratified by an infant's ability to breastfeed normally at birth.

**RESULTS:**

The mean  $\pm$  SD time from birth to initiation of breastfeeding was  $30.6 \pm 27.9$  hours. **Only 2,535 (10.0%) of women reported initiating breastfeeding in the first hour after birth and 10,207 (40.4%) reported initiating breastfeeding in the first 12 hours after birth.** In adjusted linear regression analyses, feeding ENF was associated with a significant increase in time, in hours, to breastfeeding initiation both among children not able to breastfeed at birth (37.4; 95% CI 33.3, 41.5) and among children able to breastfeed at birth (13.3; 95% CI 12.7, 14.0).

**CONCLUSIONS:**

**Feeding ENF was strongly associated with delayed initiation of breastfeeding, even after adjusting for other related factors and stratifying on the neonate's ability to suckle normally after birth.** More research is needed to understand the impact of these findings on optimal breastfeeding in this setting. It is possible that ENF feeding and the ability to breastfeed immediately after birth are interrelated in their respective associations to suboptimal breastfeeding initiation. This study in a large population representative of other populations in rural South Asia, demonstrates significantly longer times to breastfeeding initiation than previously appreciated, with a possible important role of ENF feeding.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5143457/>

[AIDS Behav.](#) 2017 Jun;21(6):1691-1698. doi: 10.1007/s10461-016-1557-9.

**Perinatal Depression Among HIV-Infected Women in KwaZulu-Natal South Africa: Prenatal Depression Predicts Lower Rates of Exclusive Breastfeeding.**

[Tuthill EL](#)<sup>1</sup>, [Pellowski JA](#)<sup>2</sup>, [Young SL](#)<sup>3</sup>, [Butler LM](#)<sup>4,5</sup>.

**Abstract**

Exclusive breastfeeding (EBF) provides infants with optimal nutrition, and together with appropriate antiretroviral therapy has also been shown to decrease mother-to-child transmission of HIV from 45 to less than 1 %. However, rates of EBF are particularly low in South Africa, where rates of HIV are some of the highest in the world. Although perinatal depression has been identified as a potential barrier to EBF, little is known about its impact on EBF among HIV-infected women. **A cohort study was conducted as part of a pilot randomized controlled trial (RCT) examining the effect of an Information, Motivation and Behavioral skills-based intervention promoting EBF among South African women living with HIV in their third trimester (28-42 weeks) of pregnancy.** At baseline and follow-up, participants were interviewed on depression symptoms (PHQ-9), and breastfeeding intentions and behavior. Multivariate logistic regressions were conducted to determine predictors of EBF at 6-weeks postpartum. A total of 68 women were enrolled and 58 women completed both baseline and follow-up assessments. Most (80.9 %) of the sample reported at least some symptoms of depression prenatally. Rates of depression were lower postpartum (47.1 %). **In multivariate models, higher prenatal depression scores significantly predicted lower likelihood of EBF at 6-weeks postpartum after adjusting for demographics, condition, and intentions (AOR = 0.68, p < 0.05).** Postpartum depression was not a significant predictor of EBF rates (AOR = 0.99, p = 0.96). These findings demonstrate the negative impact of prenatal depression on breastfeeding behavior. Future interventions focused on depression are warranted to identify those at risk for sub-optimal EBF. Improving maternal psychosocial well-being could be a new frontier to improving infant and young child feeding and reducing pre/postnatal transmission.

[PLoS Med.](#) 2016 Oct 25;13(10):e1002159. doi: 10.1371/journal.pmed.1002159. eCollection 2016 Oct.

**Impacts on Breastfeeding Practices of At-Scale Strategies That Combine Intensive Interpersonal Counseling, Mass Media, and Community Mobilization: Results of Cluster-Randomized Program Evaluations in Bangladesh and Viet Nam.**

[Menon P](#)<sup>1</sup>, [Nguyen PH](#)<sup>1</sup>, [Saha KK](#)<sup>1</sup>, [Khaled A](#)<sup>1</sup>, [Kennedy A](#)<sup>1</sup>, [Tran LM](#)<sup>2</sup>, [Sanghvi T](#)<sup>2</sup>, [Hajeebhoy N](#)<sup>2</sup>, [Baker J](#)<sup>2</sup>, [Alayon S](#)<sup>3</sup>, [Afsana K](#)<sup>4</sup>, [Haque R](#)<sup>4</sup>, [Frongillo EA](#)<sup>5</sup>, [Ruel MT](#)<sup>1</sup>, [Rawat R](#)<sup>1</sup>.

**Abstract**

**BACKGROUND:**

Despite recommendations supporting optimal breastfeeding, the number of women practicing exclusive breastfeeding (EBF) remains low, and few interventions have demonstrated implementation and impact at scale. **Alive & Thrive was implemented over a period of 6 y (2009-2014) and aimed to improve breastfeeding practices through intensified interpersonal counseling (IPC), mass media (MM), and community mobilization (CM) intervention components delivered at scale in the context of policy advocacy (PA) in Bangladesh and Viet Nam.** In Bangladesh, IPC was delivered through a large non-governmental health program; in Viet Nam, it was integrated into government health facilities. This study evaluated the population-level impact of intensified IPC, MM, CM, and PA (intensive) compared to standard nutrition counseling and less intensive MM, CM, and PA (non-intensive) on breastfeeding practices in these two countries.

**METHODS AND FINDINGS:**

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A cluster-randomized evaluation design was employed in each country. For the evaluation sample, 20 sub-districts in Bangladesh and 40 communes in Viet Nam were randomized to either the intensive or the non-intensive group. Cross-sectional surveys (n ~ 500 children 0-5.9 mo old per group per country) were implemented at baseline (June 7-August 29, 2010, in Viet Nam; April 28-June 26, 2010, in Bangladesh) and endline (June 16-August 30, 2014, in Viet Nam; April 20-June 23, 2014, in Bangladesh). Difference-in-differences estimates (DDEs) of impact were calculated, adjusting for clustering. In Bangladesh, improvements were significantly greater in the intensive compared to the non-intensive group for the proportion of women who reported practicing EBF in the previous 24 h (DDE 36.2 percentage points [pp], 95% CI 21.0-51.5,  $p < 0.001$ ; prevalence in intensive group rose from 48.5% to 87.6%) and engaging in early initiation of breastfeeding (EIBF) (16.7 pp, 95% CI 2.8-30.6,  $p = 0.021$ ; 63.7% to 94.2%). In Viet Nam, EBF increases were greater in the intensive group (27.9 pp, 95% CI 17.7-38.1,  $p < 0.001$ ; 18.9% to 57.8%); EIBF declined (60.0% to 53.2%) in the intensive group, but less than in the non-intensive group (57.4% to 40.6%; DDE 10.0 pp, 95% CI -1.3 to 21.4,  $p = 0.072$ ). Our impact estimates may underestimate the full potential of such a multipronged intervention because the evaluation lacked a "pure control" area with no MM or national/provincial PA.

### CONCLUSIONS:

**At-scale interventions combining intensive IPC with MM, CM, and PA had greater positive impacts on breastfeeding practices in Bangladesh and Viet Nam than standard counseling with less intensive MM, CM, and PA.** To our knowledge, this study is the first to document implementation and impacts of breastfeeding promotion at scale using rigorous evaluation designs. Strategies to design and deliver similar programs could improve breastfeeding practices in other contexts.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5079648/>

Acta Paediatr. 2017 Jan;106(1):49-54. doi: 10.1111/apa.13601. Epub 2016 Oct 28.

### Effect of a randomised exclusive breastfeeding counselling intervention nested into the MINIMat prenatal nutrition trial in Bangladesh.

Khan AI<sup>1</sup>, Kabir I<sup>1</sup>, Eneroth H<sup>2</sup>, El Arifeen S<sup>1</sup>, Ekström EC<sup>2</sup>, Frongillo EA<sup>3</sup>, Persson LÅ<sup>2</sup>.

### AIM:

It is unknown whether maternal malnutrition reduces the effect of counselling on exclusive breastfeeding. This study evaluated the effect of breastfeeding counselling on the duration of exclusive breastfeeding, and whether the timing of prenatal food and different micronutrient supplements further prolonged this duration.

### METHODS:

Pregnant women in Matlab, Bangladesh, were randomised to receive daily food supplements of 600 kcal at nine weeks of gestation or at the standard 20 weeks. They also were allocated to either 30 mg of iron and 400 µg folic acid, or the standard programme 60 mg of iron and folic acid or multiple micronutrients. At 30 weeks of gestation, 3188 women were randomised to receive either eight breastfeeding counselling sessions or the usual health messages.

### RESULTS:

**The median duration of exclusive breastfeeding was 135 days in the counselling group and 75 days in the usual health message group ( $p < 0.001$ ). Prenatal supplements did not modify the effects of counselling.** Women in the usual health message group who were randomised to multiple micronutrients exclusively breastfed for 12 days longer than mothers receiving the standard iron-folate combination ( $p = 0.003$ ).

### CONCLUSION:



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Breastfeeding counselling increased the duration of exclusive breastfeeding by 60 days. This duration was not influenced by the supplements.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215617/>

### Community nutrition and agriculture

[Food Nutr Bull.](#) 2016 Nov 11. pii: 0379572116676427. [Epub ahead of print]

#### **Combining Home Garden, Poultry, and Nutrition Education Program Targeted to Families With Young Children Improved Anemia Among Children and Anemia and Underweight Among Nonpregnant Women in Nepal.**

[Osei A](#)<sup>1</sup>, [Pandey P](#)<sup>2</sup>, [Nielsen J](#)<sup>3</sup>, [Pries A](#)<sup>4</sup>, [Spiro D](#)<sup>5</sup>, [Davis D](#)<sup>2</sup>, [Quinn V](#)<sup>3</sup>, [Haselow N](#)<sup>4</sup>.

#### **BACKGROUND:**

The impact of food-based interventions on child and maternal anthropometry and anemia has not been adequately studied.

#### **OBJECTIVE:**

This study tested the effect of an enhanced homestead food production (EHFP) program consisting of home garden, poultry raising, and nutrition education implemented over 2.5 years versus control (no intervention) on anthropometry and anemia among children (12-48 months) and their mothers.

#### **METHODS:**

An unblinded cluster-randomized controlled trial involving pre- and post-surveys with independent samples was conducted in rural areas of Baitadi District, Nepal. Data (including weight, height/length, and hemoglobin) were obtained from 2106 and 2614 mother-child pairs at baseline and follow-up, respectively. Changes in outcome variables (stunting, underweight, wasting, and anemia among children and underweight and anemia among mothers) were compared between the study groups using mixed-effects logistic regression models.

#### **RESULTS:**

**At follow-up, anemia was significantly lower among children (odds ratio, OR [95% confidence interval, CI]: 0.76 [0.59-0.98]) and mothers (OR [95% CI]: 0.62 [0.48-0.82]) in the treatment group compared to the control. Underweight was lower among mothers in the treatment group compared to the control (OR [95% CI]: 0.61 [0.46-0.82]).** There was no impact on child anthropometry.

#### **CONCLUSION:**

The EHFP intervention improved anemia among children aged 12 to 48 months and their mothers in Baitadi District of Nepal. The intervention also reduced underweight among these women, but had no impact on child growth, in this district.

[Br J Nutr.](#) 2016 Oct;116(8):1457-1468. Epub 2016 Oct 5.

#### **Nutrition education linked to agricultural interventions improved child dietary diversity in rural Cambodia.**

[Reinbott A](#)<sup>1</sup>, [Schelling A](#)<sup>1</sup>, [Kuchenbecker J](#)<sup>1</sup>, [Jeremias T](#)<sup>2</sup>, [Russell I](#)<sup>3</sup>, [Kevanna O](#)<sup>4</sup>, [Krawinkel MB](#)<sup>1</sup>, [Jordan I](#)<sup>1</sup>.

#### **Abstract**

Poor infant and young child feeding (IYCF) practices are major determinants of chronic malnutrition. The main objective of this study was to assess the impact of a nutrition education (NE) programme aimed at promoting improved IYCF behaviours in combination with an



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agriculture intervention on children's dietary diversity and nutritional status. From 2012 to 2014, a cluster randomised trial was rolled out in Cambodia in the context of an agriculture and nutrition project of the FAO of the UN. The cross-sectional baseline study was carried out in sixteen pre-selected communes in 2012. Restricted randomisation allotted the communes to either intervention (NE and agriculture intervention) or comparison arms (agriculture intervention only). The impact survey was conducted as a census in all FAO project villages in 2014. Caregivers of children aged 0-23 months were interviewed using standardised questions on socio-economic status and dietary diversity (24-h recall). Anthropometric measurements were taken. A difference-in-differences model was applied. The sample comprised 743 households with children  $\geq 6$  months of age at baseline and 921 at impact. After 1 year of NE, 69 % of the intervention households reported to have participated in the NE. Estimated mean child dietary diversity was significantly different at impact between comparison and intervention (3.6 and 3.9, respectively). In particular, the consumption of pro-vitamin A-rich foods and other fruits and vegetables increased. No treatment effects on height-for-age Z-scores could be shown. NE led to improvements in children's diets. For effects on growth, it is assumed that longer NE activities are required to achieve sustainable behaviour change of age-appropriate infant feeding.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5082286/>

[Asia Pac J Clin Nutr.](#) 2017 Jan;26(1):97-103. doi: 10.6133/apjcn.102015.10.

### **Local food supplementation and psychosocial stimulation improve linear growth and cognitive development among Indonesian infants aged 6 to 9 months.**

[Helmizar H](#)<sup>1,2</sup>, [Jalal F](#)<sup>3</sup>, [Lipoeto NI](#)<sup>3</sup>, [Achadi EL](#)<sup>4</sup>.

#### **BACKGROUND AND OBJECTIVES:**

To evaluate the effect of culturally-relevant food supplementation and psychosocial stimulation on infant growth and development.

#### **METHODS AND STUDY DESIGN:**

A community-based randomized controlled trial was conducted in 40 clusters from 5 selected villages in Tanah Datar District of West Sumatera, Indonesia. We assessed 355 infants aged 6 to 9 months at the beginning of the study. **The infants were divided into 4 groups: 1) Food Supplementation (FS); 2) Psychosocial Stimulation (PS); 3) Food Supplementation and Psychosocial Stimulation (FS+PS); and 4) Control Group (CG).** The formula food supplement was comprised of a variety of local food sources (local MP-ASI) and adjusted for the local habits. The quality of psychosocial stimulation was assessed with the Infant HOME inventory method. Progress at 6 months was assessed by anthropometry and the Bayley scores of cognition, language and motor function.

#### **RESULTS:**

**There were improvements in linear growth, cognitive and motor development of children in the FS ( $p < 0.05$ ) and the FS+PS ( $p < 0.01$ ) groups compared to the CG.** After six months of intervention, mean length increased to  $6.86 \pm 2.08$  cm and  $6.66 \pm 2.41$  cm for FS and FS+PS respectively ( $p < 0.05$ ). With the combination of food supplementation and psychosocial stimulation (FS+PS), cognitive development increased to  $21.4 \pm 12.2$  points (effect size 0.56) ( $p < 0.01$ ) and motor development increased to  $20.7 \pm 18.4$  points (effect size 0.50) ( $p < 0.001$ ).

#### **CONCLUSION:**

Combined intervention with local food supplementation and psychosocial stimulation improved infant growth, cognitive and motor development.

Free access: <http://apjcn.nhri.org.tw/server/APJCN/26/1/97.pdf>

[PLoS Med.](#) 2017 May 23;14(5):e1002305. doi: 10.1371/journal.pmed.1002305. eCollection 2017 May.

**Impact evaluation of different cash-based intervention modalities on child and maternal nutritional status in Sindh Province, Pakistan, at 6 mo and at 1 y: A cluster randomised controlled trial.**

[Fenn B](#)<sup>1</sup>, [Colbourn T](#)<sup>2</sup>, [Dolan C](#)<sup>1</sup>, [Pietzsch S](#)<sup>3</sup>, [Sangrasi M](#)<sup>4</sup>, [Shoham J](#)<sup>1</sup>.

**BACKGROUND:**

Cash-based interventions (CBIs), offer an interesting opportunity to prevent increases in wasting in humanitarian aid settings. However, questions remain as to the impact of CBIs on nutritional status and, therefore, how to incorporate them into emergency programmes to maximise their success in terms of improved nutritional outcomes. This study evaluated the effects of three different CBI modalities on nutritional outcomes in children under 5 y of age at 6 mo and at 1 y.

**METHODS AND FINDINGS:**

We conducted a **four-arm parallel longitudinal cluster randomised controlled trial in 114 villages in Dadu District, Pakistan**. The study included poor and very poor households ( $n = 2,496$ ) with one or more children aged 6-48 mo ( $n = 3,584$ ) at baseline. All four arms had equal access to an Action Against Hunger-supported programme. **The three intervention arms were as follows: standard cash (SC), a cash transfer of 1,500 Pakistani rupees (PKR) (approximately US\$14; 1 PKR = US\$0.009543); double cash (DC), a cash transfer of 3,000 PKR; or a fresh food voucher (FFV) of 1,500 PKR; the cash or voucher amount was given every month over six consecutive months. The control group (CG) received no specific cash-related interventions.** The median total household income for the study sample was 8,075 PKR (approximately US\$77) at baseline. We hypothesized that, compared to the CG in each case, FFVs would be more effective than SC, and that DC would be more effective than SC-both at 6 mo and at 1 y-for reducing the risk of child wasting. Primary outcomes of interest were prevalence of being wasted (weight-for-height z-score [WHZ]  $< -2$ ) and mean WHZ at 6 mo and at 1 y. **The odds of a child being wasted were significantly lower in the DC arm after 6 mo (odds ratio [OR] = 0.52; 95% CI 0.29, 0.92;  $p = 0.02$ ) compared to the CG.** Mean WHZ significantly improved in both the FFV and DC arms at 6 mo (FFV: z-score = 0.16; 95% CI 0.05, 0.26;  $p = 0.004$ ; DC: z-score = 0.11; 95% CI 0.00, 0.21;  $p = 0.05$ ) compared to the CG. **Significant differences on the primary outcome were seen only at 6 mo.** All three intervention groups showed similar significantly lower odds of being stunted (height-for-age z-score [HAZ]  $< -2$ ) at 6 mo (DC: OR = 0.39; 95% CI 0.24, 0.64;  $p < 0.001$ ; FFV: OR = 0.41; 95% CI 0.25, 0.67;  $p < 0.001$ ; SC: OR = 0.36; 95% CI 0.22, 0.59;  $p < 0.001$ ) and at 1 y (DC: OR = 0.53; 95% CI 0.35, 0.82;  $p = 0.004$ ; FFV: OR = 0.48; 95% CI 0.31, 0.73;  $p = 0.001$ ; SC: OR = 0.54; 95% CI 0.36, 0.81;  $p = 0.003$ ) compared to the CG. Significant improvements in height-for-age outcomes were also seen for severe stunting (HAZ  $< -3$ ) and mean HAZ. An unintended outcome was observed in the FFV arm: a negative intervention effect on mean haemoglobin (Hb) status (-2.6 g/l; 95% CI -4.5, -0.8;  $p = 0.005$ ). Limitations of this study included the inability to mask participants or data collectors to the different interventions, the potentially restrictive nature of the FFVs, not being able to measure a threshold effect for the two different cash amounts or compare the different quantities of food consumed, and data collection challenges given the difficult environment in which this study was set.

**CONCLUSIONS:**

**In this setting, the amount of cash given was important. The larger cash transfer had the greatest effect on wasting, but only at 6 mo.** Impacts at both 6 mo and at 1 y were seen for height-based growth variables regardless of the intervention modality, indicating a trend toward nutrition resilience. Purchasing restrictions applied to food-based voucher transfers could have unintended effects, and their use needs to be carefully planned to avoid this.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5441577/>

[J Nutr.](#) 2017 Jul;147(7):1410-1417. doi: 10.3945/jn.117.247858. Epub 2017 May 24.

**Unconditional Cash Transfers Do Not Prevent Children's Undernutrition in the Moderate Acute Malnutrition Out (MAM'Out) Cluster-Randomized Controlled Trial in Rural Burkina Faso.**

[Houngbe F](#)<sup>1,2</sup>, [Tonguet-Papucci A](#)<sup>3,2,4</sup>, [Altare C](#)<sup>3</sup>, [Ait-Aissa M](#)<sup>3</sup>, [Huneau JF](#)<sup>4</sup>, [Huybregts L](#)<sup>5</sup>, [Kolsteren P](#)<sup>2</sup>.

**Abstract**

Background: Limited evidence is available on the impact that unconditional cash transfer (UCT) programs can have on child nutrition, particularly in West Africa, where child undernutrition is still a public health challenge.

Objective: This study examined the impact of a multiannual, seasonal UCT program to reduce the occurrence of wasting (weight-for-height, midupper arm circumference), stunting (height-for-age), and morbidity among children <36 mo old in Tapoa Province, in the eastern region of Burkina Faso.

Methods: The study was designed as a 2-arm cluster-randomized controlled trial, with 32 villages randomly assigned to either the intervention or the control group. The study population comprised households that were classified as poor or very poor according to household economy approach criteria and that had  $\geq 1$  child <1 y of age at inclusion. The intervention consisted of seasonal UCTs, provided monthly from July to November, over 2 y (2013 and 2014). A monthly allowance of 10,000 West African Financial Community of Africa francs (~ US\$17) was given by mobile phone to mothers in participating households. Anthropometric measurements and morbidity were recorded on a quarterly basis.

Results: **We found no evidence that multiannual, seasonal UCTs reduced the cumulative incidence of wasting in young children** [incidence rate ratio: 0.92 (95% CI: 0.64, 1.32);  $P = 0.66$ ]. We observed no significant difference ( $P > 0.05$ ) in children's anthropometric measurements and stunting between the 2 groups at the end point. However, children in the intervention group had a lower risk [21% (95% CI: 18.6%, 21.3%);  $P < 0.001$ ] of self-reported respiratory tract infections than did children in the control group. Conclusions: We found that seasonal UCTs in the framework of safety nets did not result in a significant decrease in the incidence of acute malnutrition among children in Tapoa Province. Cash transfers combined with complementary interventions targeted to child nutrition and health should be investigated further.

[J Nutr.](#) 2016 Sep;146(9):1793-800. doi: 10.3945/jn.116.233684. Epub 2016 Jul 27.

**A Conditional Cash Transfer Program in the Philippines Reduces Severe Stunting.**

[Kandpal E](#)<sup>1</sup>, [Alderman H](#)<sup>2</sup>, [Friedman J](#)<sup>3</sup>, [Filmer D](#)<sup>3</sup>, [Onishi J](#)<sup>4</sup>, [Avalos J](#)<sup>5</sup>.

**Abstract**

**BACKGROUND:**

**Pantawid, a conditional cash transfer (CCT) program in the Philippines, provided grants conditioned on health-related behaviors for children aged 0-5 y and schooling for those aged 10-14 y.**

**OBJECTIVE:**

We investigated whether Pantawid improved anthropometric measurements in children aged 6-36 mo.

### METHODS:

We estimated cross-sectional intention-to-treat effects using a 2011 cluster-randomized trial across 130 villages-65 treated and 65 control-with data collected after 31 mo of implementation. Anthropometry characteristics were measured for 241 children in treated areas and 244 children in control areas. Health service use for children aged 6-36 mo and dietary intake for those aged 6-60 mo also were measured. Outcome variables were height-for-age z scores (HAZs) and weight-for-age z scores (WAZs), stunting, severe stunting, underweight, and severely underweight. Impact also was assessed on perinatal care, institutional delivery, presence of skilled birth attendant, breastfeeding practices, immunization, growth monitoring and deworming, care-seeking, and children's intake of protein-rich foods.

### RESULTS:

**Pantawid was associated with a significant reduction in severe stunting** [ $<-3$  SD from WHO standards for healthy children;  $\beta = -10.2$  percentage points (95% CI -18.8, -1.6 percentage points);  $P = 0.020$ ] as well as a marginally significant increase in HAZs [ $\beta = 0.284$  SDs (95% CI -0.033, 0.602 SDs);  $P = 0.08$ ]. WAZs, stunting, underweight, and severely underweight status did not change. Concomitantly, several measures of health-seeking behavior increased significantly.

### CONCLUSIONS:

**To our knowledge, Pantawid is one of few CCT programs worldwide that significantly reduced severe stunting in children aged 6-36 mo; changes in key parenting practices, including children's intake of protein-rich foods and care-seeking behavior, were concurrent.**

[Am J Clin Nutr.](#) 2016 Dec;104(6):1616-1627. Epub 2016 Nov 2.

### [Linear growth trajectories in Zimbabwean infants.](#)

[Gough EK](#)<sup>1</sup>, [Moodie EE](#)<sup>1</sup>, [Prendergast AJ](#)<sup>2,3</sup>, [Ntozini R](#)<sup>2</sup>, [Moulton LH](#)<sup>2,4</sup>, [Humphrey JH](#)<sup>2,4</sup>, [Manges AR](#)<sup>5</sup>.

### BACKGROUND:

Undernutrition in early life underlies 45% of child deaths globally. Stunting malnutrition (suboptimal linear growth) also has long-term negative effects on childhood development. Linear growth deficits accrue in the first 1000 d of life. Understanding the patterns and timing of linear growth faltering or recovery during this period is critical to inform interventions to improve infant nutritional status.

### OBJECTIVE:

We aimed to identify the pattern and determinants of linear growth trajectories from birth through 24 mo of age in a cohort of Zimbabwean infants.

### DESIGN:

We performed a secondary analysis of longitudinal data from a subset of 3338 HIV-unexposed infants in the Zimbabwe Vitamin A for Mothers and Babies trial. We used k-means clustering for longitudinal data to identify linear growth trajectories and multinomial logistic regression to identify covariates that were associated with each trajectory group.

### RESULTS:

For the entire population, the mean length-for-age z score declined from -0.6 to -1.4 between birth and 24 mo of age. Within the population, 4 growth patterns were identified that were each characterized by worsening linear growth restriction but varied in the timing and severity of growth declines. In our multivariable model, 1-U increments in maternal height and education and infant birth weight and length were associated with greater relative odds of membership in the least-growth restricted groups (A and B) and reduced odds of membership in the more-

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growth restricted groups (C and D). Male infant sex was associated with reduced odds of membership in groups A and B but with increased odds of membership in groups C and D.

### CONCLUSION:

In this population, all children were experiencing growth restriction but differences in magnitude were influenced by maternal height and education and infant sex, birth weight, and birth length, which suggest that key determinants of linear growth may already be established by the time of birth.

## Obesity

[J Clin Diagn Res.](#) 2016 Dec;10(12):SC24-SC28. doi: 10.7860/JCDR/2016/23766.9116. Epub 2016 Dec 1.

### School Based Multicomponent Intervention for Obese Children in Udupi District, South India - A Randomized Controlled Trial.

[Nayak BS<sup>1</sup>](#), [Bhat VH<sup>2</sup>](#).

#### Abstract

#### INTRODUCTION:

Childhood obesity and overweight is a global epidemics and has been increasing in the developing countries. Childhood obesity is linked with increased mortality and morbidity independent of adult obesity. Declining physical activity, access to junk food and parenting style are the major determinants of overweight in children. Thus, there is a need for increasing the physical activity of children, educating the parents as well as the children on lifestyle modification. This can be achieved through implementation of multicomponent intervention.

#### AIM:

**To evaluate the effectiveness of multicomponent intervention on improving the lifestyle practices, reducing the body fat and improving the self esteem of obese children from selected schools of Udupi District, South India.**

#### MATERIALS AND METHODS:

**A sample of 120 obese children were enrolled for multicomponent intervention.** The components of multicomponent intervention were: education provided to the obese children on lifestyle modification, education of the parents and increasing the physical education activity of these children in the form of aerobics under the supervision of physical education teacher. There was an attrition of 25% in the intervention group. Thus the final sample in the intervention group was 90. **Total sample of 131 overweight/ obese children enrolled as controls.** There was an attrition of 20.61% in the control group. Thus, the final sample in the control group was 104. Intervention group received the multicomponent intervention for six month.

#### RESULTS:

Mixed Method Repeated measures Ananalysis of Variance (ANOVA) was applied for analysis of data. **Results indicated that the intervention was effective in reducing the Body Mass Index (BMI), triceps, biceps, subscapular skin fold thickness of obese children. The intervention was also effective in improving the lifestyle practices and self-esteem of obese children.**

#### CONCLUSION:

Overweight/obese children need to control diet and perform vigorous exercise at least for 20 minutes a day to reduce the excess fat and maintain their body fat level.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5296541/>



### Comment

*The BMI in the intervention group was 24.9 (+/- 3.5) at baseline, and reduced to 22.8 (+/-3.5) after the 6 months of the intervention. BMI cut-offs for overweight and obesity change with age, and Z-scores are more useful to report. The average age was 14-16, where a BMI 2 SDs above the mean is 25.9 to 28.6. WHO BMI tables and growth charts are available at:*

[http://www.who.int/growthref/who2007\\_bmi\\_for\\_age/en/](http://www.who.int/growthref/who2007_bmi_for_age/en/)

## Oncology

(see also HIV – management of HIV related conditions)

[Clin Microbiol Infect.](#) 2017 Mar;23(3):173-178. doi: 10.1016/j.cmi.2016.11.001. Epub 2016 Nov 14.

### **Efficacy and safety of withholding antimicrobial treatment in children with cancer, fever and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial.**

[Santolaya ME](#)<sup>1</sup>, [Alvarez AM](#)<sup>2</sup>, [Acuña M](#)<sup>3</sup>, [Avilés CL](#)<sup>4</sup>, [Salgado C](#)<sup>5</sup>, [Tordecilla J](#)<sup>3</sup>, [Varas M](#)<sup>2</sup>, [Venegas M](#)<sup>6</sup>, [Villarroel M](#)<sup>1</sup>, [Zubieta M](#)<sup>5</sup>, [Toso A](#)<sup>7</sup>, [Bataszew A](#)<sup>7</sup>, [Farfán MJ](#)<sup>7</sup>, [de la Maza V](#)<sup>7</sup>, [Vergara A](#)<sup>8</sup>, [Valenzuela R](#)<sup>7</sup>, [Torres JP](#)<sup>9</sup>.

#### **OBJECTIVES:**

To determine efficacy and safety of withholding antimicrobials in children with cancer, fever and neutropenia (FN) with a demonstrated respiratory viral infection.

#### **METHODS:**

Prospective, multicentre, randomized study in children presenting with FN at five hospitals in Santiago, Chile, evaluated at admission for diagnosis of bacterial and viral pathogens including PCR-microarray for 17 respiratory viruses. **Children positive for a respiratory virus, negative for a bacterial pathogen and with a favourable evolution after 48 h of antimicrobial therapy were randomized to either maintain or withhold antimicrobials.** Primary endpoint was percentage of episodes with uneventful resolution. Secondary endpoints were days of fever/hospitalization, bacterial infection, sepsis, admission to paediatric intensive care unit (PICU) and death.

#### **RESULTS:**

A total of 319 of 951 children with FN episodes recruited between July 2012 and December 2015 had a respiratory virus as a unique identified microorganism, of which 176 were randomized, 92 to maintain antimicrobials and 84 to withdraw. Median duration of antimicrobial use was 7 days (range 7-9 days) versus 3 days (range 3-4 days), with similar frequency of uneventful resolution (89/92 (97%) and 80/84 (95%), respectively, not significant; OR 1.48; 95% CI 0.32-6.83, p 0.61), and similar number of days of fever (2 versus 1), days of hospitalization (6 versus 6) and bacterial infections throughout the episode (2%-1%), with one case of sepsis requiring admission to PICU in the group that maintained antimicrobials, without any deaths.

#### **CONCLUSIONS:**

The reduction of antimicrobials in children with FN and respiratory viral infections, based on clinical and microbiological/molecular diagnostic criteria, should favour the adoption of evidence-based management strategies in this population.



[Trop Doct.](#) 2016 Jul;46(3):142-8. doi: 10.1177/0049475515617571. Epub 2015 Nov 25.

**A clinical evaluation of efficacy and safety of cefepime monotherapy versus piperacillin-tazobactam in patients of paediatric age group with febrile neutropenia in a tertiary care centre of north India.**

[Aamir M](#)<sup>1</sup>, [Abrol P](#)<sup>2</sup>, [Sharma D](#)<sup>3</sup>, [Punia H](#)<sup>1</sup>.

**OBJECTIVE:**

To evaluate clinically the efficacy and safety in northern India of cefepime monotherapy versus piperacillin-tazobactam in patients of paediatric age group with febrile neutropenia.

**MATERIAL AND METHODS:**

Children aged  $\leq 18$  years admitted febrile with chemotherapy-induced neutropenia were randomised into two groups comprising 20 cases in each group viz. **CEF (receiving cefepime only) and PIP-TAZO (receiving piperacillin-tazobactam)**. Based on clinical and laboratory tests, patients were classified into: microbiologically documented infections (MDI); clinically documented infections (CDI); and unexplained fever (UF). They were assessed for clinical signs and symptoms as well as laboratory parameters at the time of enrolment and subsequently on days 3 and 7.

**RESULTS:**

Incidence of MDI, CDI and UF were 22.5%, 47.5% and 30%, respectively. The mean duration of neutropenia (in days) was  $5.45 \pm 2.1$  in the PIP-TAZO group and  $5.5 \pm 1.5$  in the CEF group ( $P = 0.305$ ). The success rate defined as clearing infection effectively and improvement of neutropenia was comparable ( $P = 0.705$ ). There was a mortality rate of 20% in the PIP-TAZO group as compared to 10% in the CEF group.

**CONCLUSION:**

We conclude that cefepime monotherapy and piperacillin-tazobactam are equally efficacious and safe in treating patients with febrile neutropenia. Empirical monotherapy with cefepime would prevent an unnecessary extra economic burden as well as avoiding the serious adverse or toxic effects of multi-drug regimes, especially in low- and middle-income countries.

**Comment**

*Sample size too small for any meaningful conclusion*

[Pediatr Blood Cancer.](#) 2017 Feb;64(2):234-241. doi: 10.1002/pbc.26142. Epub 2016 Oct 3.

**Treatment for childhood acute lymphoblastic leukemia in Taiwan: Taiwan Pediatric Oncology Group ALL-2002 study emphasizing optimal reinduction therapy and central nervous system preventive therapy without cranial radiation.**

[Li MJ](#)<sup>1,2</sup>, [Liu HC](#)<sup>3</sup>, [Yen HJ](#)<sup>4</sup>, [Jaing TH](#)<sup>5</sup>, [Lin DT](#)<sup>1</sup>, [Yang CP](#)<sup>5</sup>, [Lin KH](#)<sup>1</sup>, [Hung IJ](#)<sup>5</sup>, [Jou ST](#)<sup>1</sup>, [Lu MY](#)<sup>1</sup>, [Hsiao CC](#)<sup>6</sup>, [Peng CT](#)<sup>7,8</sup>, [Chang TT](#)<sup>9</sup>, [Wang SC](#)<sup>10</sup>, [Lin MT](#)<sup>10</sup>, [Chen JS](#)<sup>11</sup>, [Chang TK](#)<sup>12</sup>, [Hung GY](#)<sup>4</sup>, [Wu KH](#)<sup>7</sup>, [Yang YL](#)<sup>13</sup>, [Chang HH](#)<sup>1</sup>, [Chen SH](#)<sup>5</sup>, [Yeh TC](#)<sup>3</sup>, [Cheng CN](#)<sup>11</sup>, [Lin PC](#)<sup>14</sup>, [Chiou SS](#)<sup>14</sup>, [Sheen JM](#)<sup>6</sup>, [Cheng SN](#)<sup>15</sup>, [Chen SH](#)<sup>16</sup>, [Chang YH](#)<sup>17</sup>, [Ho WL](#)<sup>1,18,19</sup>, [Chao YH](#)<sup>20</sup>, [Chen RL](#)<sup>21</sup>, [Chen BW](#)<sup>21</sup>, [Wang JL](#)<sup>22</sup>, [Hsieh YL](#)<sup>23</sup>, [Liao YM](#)<sup>14</sup>, [Yang SH](#)<sup>24</sup>, [Chang WH](#)<sup>25</sup>, [Chao YY](#)<sup>25</sup>, [Liang DC](#)<sup>3</sup>.

**BACKGROUND:**

Reinduction therapy has improved the outcomes in children with acute lymphoblastic leukemia (ALL). We sought to determine the optimal course(s) of reinduction therapy for standard-risk (SR, or "low-risk" in other groups) patients. Also, we evaluated outcomes using triple intrathecal therapy without cranial radiation (CrRT) for central nervous system (CNS) preventive therapy.

**PROCEDURE:**

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From 2002 to 2012, all newly diagnosed children with ALL in Taiwan were enrolled in Taiwan Pediatric Oncology Group ALL-2002 protocol. SR patients were randomized to receive single or double reinduction courses. The patients enrolled before 2009 received CrRT, while those enrolled later did not. The Kaplan-Meier method was used to estimate survival rates and the difference between two groups was compared by the two-sided log-rank test.

### RESULTS:

In 1,366 eligible patients, the 5-year overall survival (OS) was  $81.6 \pm 1.1\%$  (standard error) and 5-year event-free survival (EFS) was  $74.3 \pm 1.2\%$ . In SR patients, the 5-year OS for one and two reinduction courses was  $91.6 \pm 2.1\%$  and  $93.7 \pm 1.8\%$ , respectively, and the 5-year EFS was  $85.2 \pm 2.7\%$  and  $89.8 \pm 2.3\%$ , respectively. There were no significant differences in survival between these two groups. Patients with MLL or BCR-ABL1 had the worst outcomes: 5-year EFS was 23.4 and 31.8% and 5-year OS was 28.6 and 44.7%, respectively. **There was no significant difference in CNS relapse or survival between the era with or without CrRT.**

### CONCLUSIONS:

For SR patients, one-course reinduction was adequate. Triple intrathecal therapy alone successfully prevented CNS relapse.

[Ophthalmology](#). 2016 Sep;123(9):1933-9. doi: 10.1016/j.ophtha.2016.05.034. Epub 2016 Jul 21.

### [Multimodal Therapy for Stage III Retinoblastoma \(International Retinoblastoma Staging System\): A Prospective Comparative Study.](#)

[Chawla B](#)<sup>1</sup>, [Hasan F](#)<sup>2</sup>, [Seth R](#)<sup>3</sup>, [Pathy S](#)<sup>4</sup>, [Pattebahadur R](#)<sup>2</sup>, [Sharma S](#)<sup>5</sup>, [Upadhyaya A](#)<sup>6</sup>, [Azad R](#)<sup>2</sup>.

### [Author information](#)

### PURPOSE:

To compare the efficacy of 2 chemotherapeutic drug combinations as part of multimodal therapy for orbital retinoblastoma.

### DESIGN:

Prospective, comparative, study.

### PARTICIPANTS:

Patients with stage III retinoblastoma (International Retinoblastoma Staging System).

### METHODS:

Demographic and clinical features were recorded at presentation. Treatment consisted of a multimodal protocol with neoadjuvant chemotherapy, enucleation, orbital external-beam radiotherapy, and adjuvant chemotherapy. **For chemotherapy, patients were randomized into 2 groups: group A patients were treated with vincristine, etoposide, and carboplatin (VEC) and group B patients were treated with carboplatin and etoposide, alternating with cyclophosphamide, idarubicin, and vincristine.** Treatment outcomes and adverse effects were recorded. Efficacy parameters were compared between the groups.

### MAIN OUTCOME MEASURES:

Survival probability, cause of death, and chemotherapy-related toxicity.

### RESULTS:

A total of 54 children were recruited (27 in each group). The mean  $\pm$  SD follow-up was  $21.3 \pm 11.34$  months. The overall Kaplan-Meier survival probability was 80% (95% confidence interval [CI], 0.67-0.89) and 42% (95% CI, 0.24-0.59) at 1 year and 4 years, respectively. There were 9 deaths in group A and 15 deaths in group B. The Kaplan-Meier survival probability at 1 year was similar between the groups: 81% (95% CI, 0.60-0.91) and 79% (95% CI, 0.58-0.9) for groups A and B, respectively. At 4 years, the survival probability for group A was higher (63% [95% CI, 0.41-0.79] vs. 25% [95% CI, 0.08-0.46] for groups A and B, respectively), with a strong trend of better survival in group A over time ( $P = 0.05$ ). The major cause of death was central nervous system relapse (8 patients in group A and 7 patients in group B). Two patients in

group B died of sepsis after febrile neutropenia. Grade 3 and grade 4 hematologic toxicities were more common in group B, with a significant difference in grade 4 neutropenia ( $P = 0.002$ ).

**CONCLUSIONS:**

This study compared the outcomes of **VEC chemotherapy** with a 5-drug combination of vincristine and carboplatin, alternating with cyclophosphamide, idarubicin, and vincristine, for stage III retinoblastoma. **The VEC combination was found to be more effective and may be recommended as neoadjuvant and adjuvant chemotherapy.**

[JAMA Oncol.](#) 2017 Apr 6. doi: 10.1001/jamaoncol.2017.0324. [Epub ahead of print]  
[Metronomic Chemotherapy vs Best Supportive Care in Progressive Pediatric Solid Malignant Tumors: A Randomized Clinical Trial.](#)  
[Pramanik R](#)<sup>1</sup>, [Agarwala S](#)<sup>2</sup>, [Gupta YK](#)<sup>3</sup>, [Thulkar S](#)<sup>4</sup>, [Vishnubhatla S](#)<sup>5</sup>, [Batra A](#)<sup>1</sup>, [Dhawan D](#)<sup>1</sup>, [Bakhshi S](#)<sup>1</sup>.

**Importance:**

Although oral metronomic chemotherapy is often used in progressive pediatric solid malignant tumors, a literature review reveals that only small single-arm retrospective or phase 1 and 2 studies have been performed. Skepticism abounds because of the lack of level 1 evidence.

**Objectives:**

To compare the effect of metronomic chemotherapy on progression-free survival (PFS) with that of placebo in pediatric patients with primary extracranial, nonhematopoietic solid malignant tumors that progress after at least 2 lines of chemotherapy.

**Design, Setting, and Participants:**

A double-blinded, placebo-controlled randomized clinical trial was conducted from October 1, 2013, through December 31, 2015, at the cancer center at All India Institute of Medical Sciences in children aged 5 to 18 years with primary extracranial, nonhematopoietic solid malignant tumors that progressed after at least 2 lines of chemotherapy and had no further curative options.

**Interventions:**

One arm received a 4-drug oral metronomic regimen of daily celecoxib and thalidomide with alternating periods of etoposide and cyclophosphamide, whereas the other arm received placebo. Disease status was assessed at baseline, 9 weeks, 18 weeks, and 27 weeks or at clinical progression.

**Main Outcomes and Measures:**

The primary end point was PFS as defined by the proportion of patients without disease progression at 6 months, and PFS duration and overall survival (OS) were secondary end points.

**Results:**

A total of 108 of the 123 patients screened were enrolled, with 52 randomized to the placebo group (median age, 15 years; 40 male [76.9%]) and 56 to the metronomic chemotherapy group (median age, 13 years; 42 male [75.0%]). At a median follow-up of 2.9 months, 100% of the patients had disease progression by 6 months in the placebo group vs 96.4% in the metronomic chemotherapy group ( $P = .24$ ). Median PFS and OS in the 2 groups was similar (hazard ratio [HR], 0.69; 95% CI, 0.47-1.03 [ $P = .07$ ] for PFS; and HR, 0.74; 95% CI, 0.50-1.09 [ $P = .13$ ] for OS). In post hoc subgroup analysis, cohorts receiving more than 3 cycles (HR for PFS, 0.46; 95% CI, 0.23-0.93;  $P = .03$ ) and those without a bone sarcoma (ie, neither primitive neuroectodermal tumor nor osteosarcoma) (HR for PFS, 0.39; 95% CI, 0.18-0.81;  $P = .01$ ) appeared to benefit from metronomic chemotherapy.

**Conclusions and Relevance:**

Metronomic chemotherapy does not improve 6-month PFS, compared with placebo, among pediatric patients with extracranial progressive solid malignant tumors. However, patients

without bone sarcoma and those able to tolerate therapy for more than 3 cycles (9 weeks) benefit.

### Comment

*Metronomic chemotherapy is based on the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, with no prolonged drug-free breaks. It is thought this may inhibit tumor growth primarily through anti-angiogenic mechanisms, while significantly reducing toxic side-effects of chemotherapy. If metronomic chemotherapy has a place it may be in certain difficult to treat solid tumours, to be integrated into proper cancer maintenance therapy protocols to control minimal residual disease and provide a good quality of life for patients living with cancer.* [https://link.springer.com/chapter/10.1007/978-3-662-43604-2\\_11](https://link.springer.com/chapter/10.1007/978-3-662-43604-2_11)

A good review of metronomic chemotherapy is in Nature:

<http://www.nature.com/nrclinonc/journal/v7/n8/full/nrclinonc.2010.82.html>

## Ophthalmology

[Medicine \(Baltimore\)](#). 2017 Mar;96(11):e6069. doi: 10.1097/MD.00000000000006069.

**[Design, methodology, and baseline data of the Personalized Addition Lenses Clinical Trial \(PACT\).](#)**

[Yu X<sup>1</sup>](#), [Zhang B](#), [Bao J](#), [Zhang J](#), [Wu G](#), [Xu J](#), [Zheng J](#), [Drobe B](#), [Chen H](#).

### BACKGROUND:

The aim of this study was to describe the design, methods, and baseline characteristics of children enrolled in the Personalized Addition lenses Clinical Trial (PACT). **PACT aims to test the myopia control efficacy of progressive addition lenses (PALs) with personalized addition values compared with standard (+2.00 D) addition PALs and single vision lenses (SVLs).**

### METHODS:

PACT is a randomized, controlled, double-masked clinical trial. **Two hundred eleven myopic Chinese children (7-12 years) were enrolled and randomized into 1 of the 3 following groups: personalized addition PALs; +2.00 addition PALs; and SVLs.** Personalized addition values were determined based on the highest addition that satisfied Sheard criterion. Axial length and other biometric data were also recorded.

### RESULTS:

At baseline, no differences were found between the right and left eyes for any of the main parameters. The enrolled children were  $9.7 \pm 1.1$  years' old with cycloplegic autorefraction (right eye [OD]:  $-2.36 \pm 0.64$  D), near phoria ( $1.0 \pm 5.0$  prism diopter esophoria), lag of accommodation ( $1.40 \pm 0.50$  D) and axial length (OD:  $24.58 \pm 0.74$  mm). The personalized addition values ranged from +0.75 to +3.00 (average  $\pm$  SD:  $2.19 \pm 0.73$  D).

### CONCLUSION:

PACT is a clinical trial evaluating whether myopia progression in children can be slowed by wearing personalized addition PALs compared with fixed addition PALs and SVLs as measured by cycloplegic autorefraction and axial length. Baseline data were comparable with those of previous myopia control studies in children. Subjects will be followed up every 6 months for 2 years.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5369877/>

[Trials](#). 2017 Apr 8;18(1):168. doi: 10.1186/s13063-017-1888-5.

**Effectiveness of a novel mobile health education intervention (Peek) on spectacle wear among children in India: study protocol for a randomized controlled trial.**

[Morjaria P](#)<sup>1</sup>, [Bastawrous A](#)<sup>2</sup>, [Murthy GVS](#)<sup>3</sup>, [Evans J](#)<sup>2</sup>, [Gilbert C](#)<sup>2</sup>.

**Author information**

**BACKGROUND:**

Uncorrected refractive errors are the commonest cause of visual loss in children despite spectacle correction being highly cost-effective. Many affected children do not benefit from correction as a high proportion do not wear their spectacles. Reasons for non-wear include parental attitudes, overprescribing and children being teased/bullied. Most school programmes do not provide health education for affected children, their peers, teachers or parents. **The Portable Eye Examination Kit (Peek) will be used in this study.** Peek has applications for measuring visual acuity with software for data entry and sending automated messages to inform providers and parents. Peek also has an application which simulates the visual blur of uncorrected refractive error (SightSim). The hypothesis is that higher proportion of children with uncorrected refractive errors in schools allocated to the Peek educational package will wear their spectacles 3-4 months after they are dispensed, and a higher proportion of children identified with other eye conditions will access services, compared with schools receiving standard school screening.

**METHODS/DESIGN:**

**Cluster randomized, double-masked trial of children with and without uncorrected refractive errors or other eye conditions. Government schools in Hyderabad, India will be allocated to intervention (Peek) or comparator (standard programme) arms before vision screening. In the intervention arm Peek will be used for vision screening,** SightSim images will be used in classroom teaching and will be taken home by children, and voice messages will be sent to parents of children requiring spectacles or referral. In both arms the same criteria for recruitment, prescribing and dispensing spectacles will be used. After 3-4 months children dispensed spectacles will be followed up to assess spectacle wear, and uptake of referrals will be ascertained. The cost of developing and delivering the Peek package will be assessed. The cost per child wearing their spectacles or accessing services will be compared.

**DISCUSSION:**

Educating parents, teachers and children about refractive errors and the importance of wearing spectacles has the potential to increase spectacle wear amongst children. Innovative, potentially scalable mobile technology (Peek) will be used to screen, provide health education, track spectacle wear and adherence to follow-up amongst children referred.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5385039/>

[Am J Ophthalmol](#). 2017 Apr;176:244-253. doi: 10.1016/j.ajo.2016.10.004. Epub 2016 Oct 27.

**Prospective, Randomized Clinical Trial of Povidone-Iodine 1.25% Solution Versus Topical Antibiotics for Treatment of Bacterial Keratitis.**

[Isenberg SJ](#)<sup>1</sup>, [Apt L](#)<sup>2</sup>, [Valenton M](#)<sup>3</sup>, [Sharma S](#)<sup>4</sup>, [Garg P](#)<sup>4</sup>, [Thomas PA](#)<sup>5</sup>, [Parmar P](#)<sup>5</sup>, [Kaliyamurthy J](#)<sup>5</sup>, [Reyes JM](#)<sup>3</sup>, [Ong D](#)<sup>3</sup>, [Christenson PD](#)<sup>6</sup>, [Del Signore M](#)<sup>7</sup>, [Holland GN](#)<sup>8</sup>.

**PURPOSE:**

To compare povidone-iodine 1.25% ophthalmic solution with topical antibiotics for treatment of bacterial keratitis in areas of the world where use of effective topical antibiotics may not be an option.

**STUDY DESIGN:**

Randomized, controlled, investigator-masked clinical trial.



**METHODS:**

We randomized **172 individuals with bacterial keratitis to topical treatment with povidone-iodine or antibiotics (neomycin-polymyxin B-gramicidin in the Philippines; ciprofloxacin 0.3% in India)**. Using survival analysis, we compared intervals from start of treatment to "presumed cure" (primary outcome measure, defined as a closed epithelial defect without associated inflammatory signs) and to "recovering" (residual epithelial defect  $<1 \text{ mm}^2$  with only minimal inflammation).

**RESULTS:**

Median interval to presumed cure in the Philippines was 7 days for povidone-iodine and 7 days for neomycin-polymyxin B-gramicidin (95% confidence interval [CI] for difference in median interval, -9.5 to 0.7 days) and in India was 12 days for povidone-iodine and 17 days for ciprofloxacin (95% CI, -35.2 to 3.2 days). Hazard ratio (HR) for presumed cure among those treated with povidone-iodine (vs antibiotics) was 1.46 in the Philippines (95% CI, 0.90-2.36;  $P = .13$ ) and 1.70 in India (95% CI, 0.73-3.94;  $P = .22$ ). Comparisons of intervals to recovering and HR for recovering also revealed no significant differences between treatment groups in either country.

**CONCLUSIONS:**

There is no significant difference between the effect of topical povidone-iodine 1.25% and topical antibiotics commonly available in the developing world for treatment of bacterial keratitis. Povidone-iodine 1.25%, which is widely available and inexpensive, can be considered for treatment of bacterial keratitis when antibiotic treatment is not practical.

**Comment**

*Povidine-iodine has long been known to be effective in the prevention of ophthalmia neonatorum, following a RCT in Kenya in 1995 (Isenberg SJ N Engl J Med 1995; 332:562-566). Povidone-iodine must be dilute, or it results in eye irritation and tearing, and reduces contact time of the PI with conjunctiva. Betadine is 7.5% iodine, while effective ophthalmic preparations have included 0.4%, 2.5% and 5%, and in this study 1.25%.*

[Acta Ophthalmol.](#) 2017 Mar;95(2):e95-e100. doi: 10.1111/aos.13220. Epub 2016 Aug 30.

**Toric intraocular lens implantation in children with developmental cataract and preexisting corneal astigmatism.**

[Ram J<sup>1</sup>](#), [Singh R<sup>1</sup>](#), [Gupta R<sup>1</sup>](#), [Bhutani G<sup>1</sup>](#), [Gupta PC<sup>1</sup>](#), [Sukhija J<sup>1</sup>](#).

**PURPOSE:**

**To evaluate the effect of toric intraocular lens (IOL) implantation on the refractive outcomes in children with cataract and preexisting corneal astigmatism.**

**METHODS:**

We included children between the age group of 8-14 years who were randomized into group I (toric) and group II (non-toric), in which toric and spherical IOLs were implanted, respectively, after phacoaspiration. Primary outcome measure was comparison of preoperative keratometric and postoperative refractive cylinder. Secondary outcome measure was comparison of pre- and postoperative visual outcome.

**RESULTS:**

This study included 21 eyes of 17 children with developmental cataract. The mean spherical power of the toric IOLs implanted in the group I was  $22.42 \pm 4.84 \text{ D}$  (range 12.50-29.00 D) and the mean cylindrical power of toric IOL was  $3.37 \pm 1.43 \text{ D}$  (range 1.50-6.00D). The mean spherical power implanted in non-toric (group II) was  $20.70 \pm 7.09 \text{ D}$  (range 10-31D). Mean preoperative keratometric cylinder in group I was  $2.99 \pm 0.96 \text{ D}$  (range 1.85-5.12 D) and in group II it was  $3.35 \pm 0.63 \text{ D}$  (range 2.03D-4.33 D) ( $p = 0.31$ ) while the mean refractive cylinder



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at one year postoperatively in group I was  $0.50 \pm 0.39$  D (range 0.00-1.00 D) and in group II it was  $2.05 \pm 0.39$  D (range 1.25D-2.50 D;  $p = 0.006$ ). Twelve months postoperatively, group I had a mean spherical equivalent (SE)  $0.41 \pm 0.26$  D (range 0.00-0.88 D) and group II had  $1.8 \pm 1.03$  D (range 0.63-4.00 D) ( $p = 0.002$ ). Uncorrected distance visual acuity (UDVA) improved from  $0.94 \log \text{MAR} \pm 0.51$  (range 0.60-2.00) to  $0.43 \log \text{MAR} \pm 0.33$  (range 0.00-1.00) in the group I at the end of 1 year and in group II, it improved from  $1.52 \log \text{MAR} \pm 1.12$  to  $0.75 \log \text{MAR} \pm 0.70$  (range 0.00-2.00) at the end of 1 year. **Corrected distant visual acuity (CDVA) improved in group I from  $0.72 \log \text{MAR} \pm 0.17$  (range 0.48-1.00) to  $0.19 \log \text{MAR} \pm 0.26$  (range 0.00- 0.78) at the end of one year while in group II, it improved from  $1.33 \pm 1.08$  (range 0.18-3.00) to  $0.49 \log \text{MAR} \pm 0.80$  (range 0.00-2.00) at the end of 1 year.**

**CONCLUSIONS:**

Toric IOL implantation in children significantly reduces postoperative astigmatism and thereby improves visual outcome.

### Note

A toric lens is a lens with different optical power and focal length in two orientations perpendicular to each other. One of the lens surfaces is shaped like a slice from a torus (a donut shaped object), while the other one usually is spherical. Toric lenses are primarily used in eyeglasses, contact lenses and intraocular lenses to correct astigmatism (see Wikipedia).

[Am J Ophthalmol](#). 2016 Aug;168:157-63. doi: 10.1016/j.ajo.2016.05.010. Epub 2016 May 20.

### **Comparison of Amniotic Membrane Transplantation and Umbilical Cord Serum in Acute Ocular Chemical Burns: A Randomized Controlled Trial.**

[Sharma N](#)<sup>1</sup>, [Singh D](#)<sup>2</sup>, [Maharana PK](#)<sup>2</sup>, [Kriplani A](#)<sup>3</sup>, [Velpandian T](#)<sup>2</sup>, [Pandey RM](#)<sup>4</sup>, [Vajpayee RB](#)<sup>5</sup>.

### **PURPOSE:**

To compare the efficacy of topical umbilical cord serum drops (UCS) and amniotic membrane transplantation (AMT) in acute ocular chemical burns.

### **DESIGN:**

Randomized controlled trial.

### **METHODS:**

setting: Tertiary care hospital.

### **STUDY POPULATION:**

Forty-five eyes with acute chemical burns of grade III, IV, and V (Dua's classification) presenting within the first week of injury were randomized into 3 groups (15 each). Patients with perforation/impending corneal perforation were excluded from the study.

### **INTERVENTION:**

Groups 1, 2, and 3 received UCS with medical therapy (MT), AMT with MT, and MT alone, respectively.

### **MAIN OUTCOME MEASURE:**

Time to complete epithelialization.

### **RESULTS:**

**The mean time to complete epithelialization was  $56.7 \pm 14.9$ ,  $22.0 \pm 10.2$ , and  $22.9 \pm 10.1$  days in MT, AMT, and UCS groups, respectively, with a significant difference between MT and AMT ( $P = .001$ ) and between MT and UCS ( $P = .001$ ), but not between UCS and AMT ( $P = .9$ ). Improvement in pain score was better with UCS than AMT ( $P$  value: .012, .002, and .012 on days 7, 14, and 21, respectively). Corneal clarity was better in the UCS group at 21 ( $P = .008$ ) and 30 days ( $P = .002$ ), but not at 3 months ( $P = .9$ ). By month 3, visual outcome, symblepharon, tear film status, and lid abnormalities were comparable between the 3 groups.**

### **CONCLUSIONS:**

UCS and AMT, as an adjuvant to standard medical therapy in acute chemical injury, are equally efficacious. **UCS has the advantage of faster improvement in corneal clarity, better pain control, and avoidance of surgery in an inflamed eye.**

### Note

Umbilical cord blood serum contains a high concentration of essential tear components, epidermal growth factors, nerve growth factors, vitamin A, fibronectin, prealbumin, insulin-like growth factors, and platelet-derived growth factors.

<https://pdfs.semanticscholar.org/512f/9247a215683c363969ad2220138d5df5e1a1.pdf>

<http://iovs.arvojournals.org/article.aspx?articleid=2126375>

*Paediatr Anaesth*. 2017 Feb;27(2):162-169. doi: 10.1111/pan.13040. Epub 2016 Nov 30.

**Anesthesia maintenance with 'induction dose only' sevoflurane during pediatric ophthalmic examination: comparison with standard low-flow technique through a randomized controlled trial.**

Datta PK<sup>1</sup>, Sinha R<sup>1</sup>, Ray BR<sup>1</sup>, Jambunathan V<sup>1</sup>, Kundu R<sup>1</sup>.

### BACKGROUND:

Sevoflurane is preferred for pediatric day care procedures. However, financial and environmental costs remain major limitations. Induction dose of sevoflurane could itself be sufficient for maintaining anesthesia with low fresh gas flow during short noninvasive procedures.

### METHODS:

Fifty children, aged 1-5 years, scheduled for ophthalmic examination under anesthesia, were randomized into two groups. All children were induced with 8% sevoflurane in O<sub>2</sub> : N<sub>2</sub> O (40 : 60). In the Group S, anesthesia was maintained with 2% sevoflurane at 1 l·min<sup>-1</sup> fresh gas flow [O<sub>2</sub> : N<sub>2</sub> O = 50 : 50]. In Group L, the sevoflurane vaporizer was turned off and fresh gas flow was reduced to 0.5 l·min<sup>-1</sup> [O<sub>2</sub> : N<sub>2</sub> O = 50 : 50]. HR, BP, MAC, BIS, total sevoflurane consumption, ocular deviation, body movement, time to laryngeal mask airway removal (T<sub>wo</sub>), and airway complications were compared between the groups. Rescue propofol bolus was used, if needed.

### RESULTS:

Median duration of examination was 14 min (IQR = 9-17) in Group S and 15 min (IQR = 10-17) in Group L. Sevoflurane consumption was lower in the Group L (7 ml) compared to Group S (9 ml) [median difference = 2 ml, P < 0.001, 95% CI = 0.96-3.04]. T<sub>wo</sub> was lower in Group L (86 s) compared to Group S (131 s) [median difference = 45 s, P = 0.002, 95% CI = 19.85-70.15]. There was no difference in hemodynamic parameters, incidence of ocular deviation, movement or airway complications, and need for rescue propofol.

### CONCLUSION:

Induction dose of sevoflurane is, in itself, adequate for maintaining anesthesia for short noninvasive ophthalmic examinations lasting approximately 15 min. This method significantly reduces sevoflurane consumption and cost.

## Trachoma

(See also Hygiene)

## Oral health / dentistry

[J Clin Diagn Res.](#) 2016 Sep;10(9):ZC56-ZC60. Epub 2016 Sep 1.

### **Efficacy of Four Fluoride Mouth Rinses on *Streptococcus mutans* in High Caries Risk Children - A Randomized Controlled Trial.**

[Perala SR<sup>1</sup>](#), [Bhupathiraju P<sup>2</sup>](#).

#### **INTRODUCTION:**

Dental caries has been traditionally described as a multifactorial disease that involves the interaction of various factors like host, agent, substrate and time. Landmark studies have established the fact that **Mutans Streptococci are the primary etiologic agents of dental caries**. The prevention of dental caries by fluoride supplements in various vehicles, such as water and toothpaste, constitutes one of the most successful prevention measures.

#### **AIM:**

The aim of the present study was to compare the clinical efficacy of four fluoride mouth rinses on *Streptococcus mutans* in high caries risk children and also to check the efficacy of the ingredient Triclosan which is present in two of the four mouth rinses.

#### **MATERIALS AND METHODS:**

The study is double blinded, consisting of 1000 children in age group 6-14yrs who were screened from residential schools. Of the total, 200 children were categorized as high caries risk group based on caries risk assessment tool form given by American Association of Pediatric Dentistry (AAPD) guidelines 2011. Prior to the study, salivary samples were collected and sent for microbial analysis to estimate *Streptococcus mutans* counts. Out of 200 salivary samples, 132 showed 10<sup>6</sup>CFU of *Streptococcus mutans* and these children were included in the study. The 132 children from each group received the assigned mouth wash for 14 consecutive days. On 15<sup>th</sup> day the salivary samples were collected and sent for microbial analysis and the obtained results were subjected to statistical analysis.

#### **RESULTS:**

**All the mouth washes showed a significant reduction in Colony Forming Units (CFU) counts of *Streptococcus mutans*.** Among the four groups Group D (S flo) showed greater percentage reduction of *Streptococcus mutans* followed by Group A (Act), B (Kidodent) and C (Zerocary). There was no statistically significant reduction of *Streptococcus mutans* among the Triclosan containing and non containing groups.

#### **CONCLUSION:**

The mean pre rinse CFU was significantly higher than post rinse CFU for all the study groups, suggesting that all the four mouth rinses were effective in decreasing the levels of *Streptococcus mutans* in the saliva. Both the Triclosan containing and non Triclosan groups showed the same amount of CFU count reduction.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5072081/>

[Int J Dent.](#) 2017;2017:5654373. doi: 10.1155/2017/5654373. Epub 2017 Mar 2.

### **Effect of Herbal and Fluoride Mouth Rinses on *Streptococcus mutans* and Dental Caries among 12-15-Year-Old School Children: A Randomized Controlled Trial.**

[Somaraj V<sup>1</sup>](#), [Shenoy RP<sup>2</sup>](#), [Shenoy Panchmal G<sup>2</sup>](#), [Kumar V<sup>3</sup>](#), [Jodalli PS<sup>2</sup>](#), [Sonde L<sup>2</sup>](#).

#### **Abstract**

To assess and compare the effect of herbal and fluoride mouth rinses on *Streptococcus mutans* count and glucan synthesis by *Streptococcus mutans* and dental caries, a parallel group placebo controlled randomized trial was conducted among 240 schoolchildren (12-15 years old).

**Participants were randomly divided and allocated into Group I (0.2% fluoride group),**

**Group II (herbal group), and Group III (placebo group).** All received 10 ml of respective mouth rinses every fortnight for a period of one year. **Intergroup and intragroup comparison were done for *Streptococcus mutans* count and glucan synthesis by *Streptococcus mutans* and dental caries. *Streptococcus mutans* count showed a statistically significant difference between Group I and Group III ( $p = 0.035$ ) and also between Group II and Group III ( $p = 0.039$ ). Glucan concentration levels showed a statistically significant difference ( $p = 0.024$ ) between Group II and Group III at 12th month.** Mean DMF scores showed no statistical difference between the three groups ( $p = 0.139$ ). No difference in the level of significance was seen in the intention-to-treat and per-protocol analysis. The present study showed that both herbal and fluoride mouth rinses, when used fortnightly, were equally effective and could be recommended for use in school-based health education program to control dental caries.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5352884/>

#### Comment

*The herbal mouthwash used in the above trial is called Freshol, which was used in another plaque reduction trial also. (Mehta S, et al. J Int Soc Prevent Curative Dentistry 2013; 3; 25-28)*

[Contemp Clin Dent](#). 2017 Jan-Mar;8(1):116-121. doi: 10.4103/ccd.ccd\_836\_16.

#### **Effect of Freeze Dried Powdered Probiotics on Gingival Status and Plaque Inhibition: A Randomized, Double-blind, Parallel Study.**

[Yousuf A<sup>1</sup>](#), [Sidiq M<sup>2</sup>](#), [Ganta S<sup>3</sup>](#), [Nagaraj A<sup>3</sup>](#), [Vishnani P<sup>4</sup>](#), [Jan I<sup>5</sup>](#).

#### **OBJECTIVE:**

The study aimed to evaluate the effectiveness of freeze dried powdered probiotics on gingival status and plaque inhibition among 12-15-year-old schoolchildren.

#### **MATERIALS AND METHODS:**

This randomized controlled trial was conducted among 12-15-year-old schoolchildren in Jaipur. **Commercially available freeze dried probiotics containing *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Bifidobacterium bifidum* and *Bifidobacterium lactis* (Prowel, Alkem Laboratories), lactic acid bacillus only (Sporolac, Sangyo), and a placebo powder calcium carbonate 250 g (Calcium Sandoz, Novartis) were assigned to two intervention groups and a placebo group each comprising 11 schoolchildren.** All subjects were instructed to mix the powder in 30 ml of water and swish once daily for 3 min, for 3 weeks. Periodontal clinical parameters were assessed by examining the subjects for Turesky-Gilmore-Glickman plaque index (PI) (Modification of Quigley-Hein PI) and gingival index at baseline, 7<sup>th</sup> day, 14<sup>th</sup> day, and 21<sup>st</sup> day.

#### **RESULTS:**

**For both the probiotic groups, a statistically significant reduction ( $P < 0.05$ ) in gingival status and plaque inhibition was recorded up to 2<sup>nd</sup> week of probiotic ingestion.** However, no significant difference was observed in the placebo group.

#### **CONCLUSION:**

The use of probiotic mouth rinses improves the oral health in children by significantly reducing the plaque and gingival scores. Further studies are warranted to prove or refute the long-term effects, means of administering probiotics and the dosages needed to achieve different preventive or therapeutic purposes.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5426143/>

**Comment**

*A very small study (11 children in each group), and with only 2 weeks follow-up.*

[J Indian Soc Pedod Prev Dent.](#) 2016 Oct-Dec;34(4):383-90. doi: 10.4103/0970-4388.191429.  
**Single- versus two-visit pulpectomy treatment in primary teeth with apical periodontitis: A double-blind, parallel group, randomized controlled trial.**  
[Bharuka SB<sup>1</sup>](#), [Mandroli PS<sup>1</sup>](#).

**CONTEXT:**

Reduction of the bacterial populations to levels compatible with periradicular tissue healing is the primary microbiological goal of the endodontic treatment of teeth with apical periodontitis. The number of visits required to treat teeth with apical periodontitis represents one of the most debatable issues in endodontics.

**OBJECTIVES:**

The objective of this study was to compare and evaluate the clinical and radiographic outcome of single- versus two-visit pulpectomy treatment in primary teeth with apical periodontitis at the end of 6-month healing period.

**SETTINGS AND DESIGN:**

A parallel group, double-blind, randomized controlled trial was carried out in 64 children aged 4-8 years. Nonvital primary teeth with apical periodontitis with enough coronal structure were selected. Sixty-four children were assigned randomly into two groups (32 children each) by block randomization, and allocation concealment was done with closed envelop method.

**METHODS AND MATERIALS:**

Group I underwent single-visit pulpectomy followed by obturation with zinc oxide eugenol (ZOE). Group II underwent conventional two-visit pulpectomy with intracanal calcium hydroxide, followed by obturation with ZOE. Postoperative clinical and radiographic evaluation was carried out at 1, 3, and 6 months after the end of the treatment.

**STATISTICAL ANALYSIS USED:**

The data were analyzed by Wilcoxon's signed rank test, Mann-Whitney U-test, and Friedman test.

**RESULTS:**

There was no statistically significant difference in clinical and radiographic outcomes in both the groups at the end of 6-month healing period.

**CONCLUSION:**

Single-visit pulpectomy can be considered as a viable option for the treatment of primary teeth with apical periodontitis.

Free access: <http://www.jisppd.com/article.asp?issn=0970-4388;year=2016;volume=34;issue=4;spage=383;epage=390;aulast=Bharuka>

[Anesth Essays Res.](#) 2017 Apr-Jun;11(2):431-438. doi: 10.4103/0259-1162.194535.  
**Comparison of a New Auto-controlled Injection System with Traditional Syringe for Mandibular Infiltrations in Children: A Randomized Clinical Trial.**  
[Deepak V<sup>1</sup>](#), [Challa RR<sup>1</sup>](#), [Kamatham R<sup>1</sup>](#), [Nuvvula S<sup>1</sup>](#).

**BACKGROUND:**

Pain in the dental operatory can have a profound effect on the behavior of children.

**AIM:**



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The aim of this study is to evaluate the pain perception while administering local infiltration, in children undergoing dental extractions, using a new auto-controlled injection system.

### **MATERIALS AND METHODS:**

Children in the age range of 6-10 years with teeth indicated for extraction were recruited and allocated to either Group I, computer-controlled injection system (auto system with special cartridge and compatible disposable 30-gauge, 10 mm needles), or Group II, traditional system (30-gauge, 10 mm needle and disposable traditional syringe). Local infiltration was administered and extraction performed after 3 min. The time of administration (TOA) of infiltrate was noted whereas anxiety and pain in both groups were assessed using the Modified Child Dental Anxiety Faces Scale simplified (MCDAS<sub>(f)</sub>), pulse rate, Faces Pain Scale-Revised (FPS-R), and Face, Legs, Activity, Cry, Consolability (FLACC) Scale.

### **RESULTS:**

The TOA was high in computer group, compared to the traditional system ( $P < 0.001^{***}$ ); however, anxiety and pain were significantly less in computer group as reported in MCDAS<sub>(f)</sub>, pulse rate, FPS-R, and FLACC ( $P < 0.001^{***}$ ).

### **CONCLUSIONS:**

Computer system created a positive and comfortable experience for the child, as well as the practitioner. The possibility of using buccal infiltration instead of inferior alveolar nerve block in children below 10 years was also demonstrated.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5490139/>

[J Dent \(Shiraz\)](#). 2017 Jun;18(2):112-117.

### **Pioneering Strategies for Relieving Dental Anxiety in Hearing Impaired Children: a Randomized Controlled Clinical Study.**

[Chandrasekhar S](#)<sup>1</sup>, [Madu GP](#)<sup>2</sup>, [Ambati NR](#)<sup>3</sup>, [Suravarapu PR](#)<sup>4</sup>, [Uppu K](#)<sup>4</sup>, [Bolla D](#)<sup>4</sup>.

### **STATEMENT OF THE PROBLEM:**

Hearing impaired children have a problem in understanding and comprehending with dental treatments. Visual language is the sensible answer of how to improve communication with them.

### **PURPOSE:**

To evaluate the applicability of dental sign language in Hearing impaired children in relieving anxiety during stressful dental treatment by improving their means of communication.

### **MATERIALS AND METHOD:**

This randomized clinical trial was carried out in the Department of Pedodontics and Preventive Dentistry which included 40 Hearing Impaired children meeting inclusion criteria. The selected children were randomly divided into the study and control group comprising of 20 each. In the control group, initial oral examination and dental treatment (oral prophylaxis and class I restoration) were performed without the use of dental sign language. In the study group, the dental sign language specific to dental treatment was educated and during their subsequent visit to the dental clinic after dental sign language reinforcement, oral prophylaxis and class I restoration were done. Subjective and objective measurements of anxiety were recorded for both groups using facial image scale (FIS), pulse oximeter and electronic blood pressure apparatus to compare for correlation. The obtained data were subjected to statistical analysis using unpaired t-test.

### **RESULTS:**

There was a statistically significant reduction in the anxiety levels ( $p < 0.05$ ) in the study group compared to the control group.

### **CONCLUSION:**



**Dental sign language was effective in reducing the level of anxiety in children who are hard of hearing.** Dental sign language was able to improve behavior positively during dental treatment and may also aid in developing a positive dental attitude among children who are hard of hearing.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5463769/>

[J Indian Soc Pedod Prev Dent.](#) 2017 Apr-Jun;35(2):143-149. doi: 10.4103/JISPPD.JISPPD\_257\_16.

**Effectiveness of two different behavioral modification techniques among 5-7-year-old children: A randomized controlled trial.**

[Vishwakarma AP<sup>1</sup>](#), [Bondarde PA<sup>1</sup>](#), [Patil SB<sup>1</sup>](#), [Dodamani AS<sup>2</sup>](#), [Vishwakarma PY<sup>2</sup>](#), [Mujawar SA<sup>1</sup>](#).

**BACKGROUND:**

Dental fear is a common, essential, and inevitable emotion that appears as a response to the stressful situation, which raises children's anxiety level, resulting in reduced demand for pediatric dental care.

**AIMS:**

(1) To compare and evaluate the effectiveness of customized tell-play-do (TPD) technique with live modeling for behavior management of children. (2) To compare the behavioral modification techniques in managing the children during their dental visits.

**MATERIALS AND METHODS:**

Ninety-eight children aged 5-7 years were enrolled in the study and randomly allocated into two groups. Phase I: first visit. Group I - children were conditioned to receive various dental procedures using live modeling followed by oral prophylaxis. Group II - TPD technique was introduced with customized playing dental objects followed by oral prophylaxis. Phase II: second visit. After 7 days interval, all the study subjects were subjected to rotary restorative treatment.

**EVALUATION:**

Heart rate, Facial Image Scale (FIS), and Venham-6-point index were used before intervention, after intervention, and during dental procedure to quantify the anxious behavior.

**RESULTS:**

All 98 children after intervention underwent oral prophylaxis on first visit and rotary restorative treatment on second visit. The average pulse rate, FIS, and Venham scale scores were significantly lower among children who received TPD intervention when compared to those who received live modeling intervention. Unpaired t-test at 5% level of significance was considered as statistical significance.

**CONCLUSIONS:**

TPD is effective in reducing children's fear and anxiety about dental treatment, children enjoy playing with customized dental object. Thus, to promote adaptive behavior, TPD could be an alternate behavioral modification technique during pediatric dentistry.

Free access: <http://www.jisppd.com/article.asp?issn=0970-4388;year=2017;volume=35;issue=2;spage=143;epage=149;aulast=Vishwakarma>

[Int J Oral Maxillofac Surg.](#) 2017 Aug;46(8):977-987. doi: 10.1016/j.ijom.2017.03.006. Epub 2017 Apr 14.

**Long-term effect of presurgical nasoalveolar molding on growth of maxillary arch in unilateral cleft lip and palate: randomized controlled trial.**

Shetty V<sup>1</sup>, Agrawal RK<sup>2</sup>, Sailer HF<sup>2</sup>.

**Abstract**

The objective of this study was to investigate the long-term effect of presurgical nasoalveolar molding (PNAM) on growth of the maxillary arch through early childhood until 6 years of age in complete unilateral cleft lip and palate (UCLP) patients presenting for PNAM at different ages. Complete UCLP patients who were treated at our centre were divided into two groups. The study group underwent PNAM and was further subdivided into three subgroups (PNAM initiated within 1 month, between 1 and 6 months, and between 6 and 12 months of age in subgroup I, II, and III, respectively). The control group did not undergo PNAM and was further subdivided into three subgroups. Patients were evaluated at T1 (first visit), T2 (before cheiloplasty), and T3 (at 6 years). Between T1 and T2, the intersegment distance (ISD) reduced significantly in the study group but increased in the control group, whereas the intercanine width (ICW) in both the study and control groups did not show significant change. Between T2 and T3, ISD and ICW were reduced significantly in the control group due to arch collapse, whereas in the study group, ISD reduced slightly with ICW remaining almost similar to noncleft norms. We conclude that reduced ISD following PNAM improves arch symmetry and stability, and thus may prevent arch collapse in the long term.

Am J Orthod Dentofacial Orthop. 2017 Mar;151(3):433-439. doi: 10.1016/j.ajodo.2016.10.019.

**Comparison of survival time and comfort between 2 clear overlay retainers with different thicknesses: A pilot randomized controlled trial.**

Zhu Y<sup>1</sup>, Lin J<sup>1</sup>, Long H<sup>1</sup>, Ye N<sup>2</sup>, Huang R<sup>1</sup>, Yang X<sup>1</sup>, Jian F<sup>1</sup>, Lai W<sup>3</sup>.

**Author information**

**INTRODUCTION:**

The objective of this 2-arm parallel trial was to compare the survival times, failure rates, and comfort of 2 clear overlay retainers with different thicknesses (0.75 and 1.00 mm).

**METHODS:**

Eighty eligible participants who had undergone orthodontic treatment at West China Stomatology Hospital of Sichuan University were recruited and randomly assigned to either the 0.75-mm group or the 1.00-mm group. Eligibility criteria included patients with central incisors, canines, and first molars and no systemic or oral disease. The main outcomes were survival time and total failure rate; the secondary outcomes were rates of different types of failure (fracture, loss, nonfitting, and abrasion); tertiary outcomes included patients' comfort levels assessed with a visual analog scale and a health survey. Randomization was accomplished by tossing a coin, with the allocations concealed in sequentially numbered, opaque, sealed envelopes, and blinding implemented among practitioners, patients, and analysts. Patients were evaluated at 1, 3, 6, and 12 months of follow-up.

**RESULTS:**

A total of 80 patients were initially recruited and randomized (42 in the 0.75-mm group, 38 in the 1.00-mm group); 72 patients completed the study and were analyzed (37 in the 0.75-mm group, 35 in the 1.00-mm group); there were 8 dropouts. Baseline characteristics were similar between the groups. At the end of the 1-year follow-up, survival time did not differ significantly between the groups (46.5 days; 95% confidence interval [CI], -10.3 -103.2;  $P = 0.111$ ). The hazard ratio was 0.77 (95% CI, 0.48-1.24;  $P = 0.281$ ). With regard to total failure rate, no statistical difference ( $P = 0.118$ ) existed between the 0.75-mm group (43.2%) and the 1.00-mm group (25.7%) (risk difference, 17.5%; 95% CI, -4.0%-39.1%). Among the different failure types, we found that fracture rates were significantly higher in the 0.75-mm group than in the

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1.00-mm group ( $P = 0.028$ ), whereas other failure types were similar between the groups (all,  $P > 0.05$ ). No clinically significant differences were found in comfort between the 2 groups. No harms were encountered.

### CONCLUSIONS:

Although the 0.75-mm group had a higher fracture rate, our results indicated no evidence that survival and comfort of retainers differ between 1.00 mm and 0.75 mm. When determining the type of retainer to be used, other factors such as retention effectiveness also should be considered.

## Poisoning and toxins

(See envenomation)

## Quality of care

[Am J Trop Med Hyg.](#) 2016 Aug 3;95(2):358-67. doi: 10.4269/ajtmh.16-0103. Epub 2016 Jun 6. **[The Impact of an Intervention to Improve Malaria Care in Public Health Centers on Health Indicators of Children in Tororo, Uganda \(PRIME\): A Cluster-Randomized Trial.](#)** [Staedke SG](#)<sup>1</sup>, [Maiteki-Sebuguzi C](#)<sup>2</sup>, [DiLiberto DD](#)<sup>3</sup>, [Webb EL](#)<sup>3</sup>, [Mugenyi L](#)<sup>4</sup>, [Mbabazi E](#)<sup>2</sup>, [Gonahasa S](#)<sup>2</sup>, [Kigozi SP](#)<sup>2</sup>, [Willey BA](#)<sup>3</sup>, [Dorsey G](#)<sup>5</sup>, [Kamya MR](#)<sup>6</sup>, [Chandler CI](#)<sup>3</sup>.

### Abstract

Optimizing quality of care for malaria and other febrile illnesses is a complex challenge of major public health importance. To evaluate the impact of an intervention aiming to improve malaria case management on the health of community children, a cluster-randomized trial was conducted from 2010-2013 in Tororo, Uganda, where malaria transmission is high. Twenty public health centers were included; 10 were randomized in a 1:1 ratio to intervention or control. Households within 2 km of health centers provided the sampling frame for the evaluation. **The PRIME intervention included training in fever case management using malaria rapid diagnostic tests (mRDTs), patient-centered services, and health center management; plus provision of mRDTs and artemether-lumefantrine.** Cross-sectional community surveys were conducted at baseline and endline ( $N = 8,766$ ), and a cohort of children was followed for approximately 18 months ( $N = 992$ ). **The primary outcome was prevalence of anemia (hemoglobin  $< 11.0$  g/dL) in children under 5 years of age in the final community survey.** The intervention was delivered successfully; however, no differences in prevalence of anemia or parasitemia were observed between the study arms in the final community survey or the cohort. **In the final survey, prevalence of anemia in children under 5 years of age was 62.5% in the intervention versus 63.1% in control (adjusted risk ratio = 1.01; 95% confidence interval = 0.91-1.13;  $P = 0.82$ ).** The PRIME intervention, focusing on training and commodities, did not produce the expected health benefits in community children in Tororo. This challenges common assumptions that improving quality of care and access to malaria diagnostics will yield health gains.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4973182/>

## Schistosomiasis

[PLoS Negl Trop Dis.](#) 2017 Feb 21;11(2):e0005400. doi: 10.1371/journal.pntd.0005400.  
eCollection 2017 Feb.

**Ultrasonographic evaluation of urinary tract morbidity in school-aged and preschool-aged children infected with *Schistosoma haematobium* and its evolution after praziquantel treatment: A randomized controlled trial.**

[Barda B](#)<sup>1,2</sup>, [Coulibaly JT](#)<sup>1,2,3,4</sup>, [Hatz C](#)<sup>2,5</sup>, [Keiser J](#)<sup>1,2</sup>.

### **BACKGROUND:**

***Schistosoma haematobium* infections are responsible for significant urinary tract (UT) complications.** Schistosomiasis control programs aim to reduce morbidity, yet the extent of morbidity in preschool-aged children and the impact of treatment on morbidity reduction are not well studied.

### **METHODOLOGY:**

Our study was embedded in a **randomized, placebo-controlled, single-blind trial in Côte d'Ivoire, which evaluated the efficacy and safety of three doses (20, 40 and 60 mg/kg) of praziquantel in school-aged (SAC) and preschool-aged (PSAC) children infected with *S. haematobium*.** Enrolled children were invited to participate in an ultrasound examination prior and six months after treatment. At these time points 3 urine samples were collected for parasitological and clinical examinations.

### **PRINCIPAL FINDINGS:**

162 PSAC and 141 SAC participated in the ultrasound examination at baseline, of which 128 PSAC and 122 SAC were present at follow-up. **At baseline 43% (70/162) of PSAC had UT morbidity, mostly at bladder level and 7% had hydronephrosis. 67% (94/141) of SAC revealed mainly moderate UT pathology, 4% presented pseudopolyps on the bladder wall, and 6% had pyelectasis. At follow up, 45% of PSAC and 58% of SAC were *S. haematobium* positive, mostly harboring light infection intensities (41% and 51%, respectively).** Microhematuria was present in 33% of PSAC and 42% of SAC and leukocyturia in 53% and 40% of PSAC and SAC, respectively. 50% (64/128) of PSAC and 58% (71/122) of SAC presented urinary tract morbidity, which was mainly mild. **A significant correlation ( $p<0.05$ ) was observed between praziquantel treatment and reversal of *S. haematobium* induced morbidity. Progression of UT pathology decreased with increasing praziquantel dosages.** A worsening of morbidity was observed among children in the placebo group.

### **CONCLUSION/SIGNIFICANCE:**

**Bladder morbidity is widespread among PSAC.** Praziquantel treatment is significantly associated with the reversal of *S. haematobium* induced morbidity, which underscores the importance of preventive chemotherapy programs. These programs should be expanded to PSAC to prevent or decrease the prevalence of morbidity in young children.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5336295/>

[PLoS Negl Trop Dis.](#) 2016 Sep 16;10(9):e0005008. doi: 10.1371/journal.pntd.0005008.  
eCollection 2016 Sep.

**Efficacy and Safety of Moxidectin, Synriam, Synriam-Praziquantel versus Praziquantel against *Schistosoma haematobium* and *S. mansoni* Infections: A Randomized, Exploratory Phase 2 Trial.**

[Barda B](#)<sup>1,2</sup>, [Coulibaly JT](#)<sup>1,2,3,4</sup>, [Puchkov M](#)<sup>5</sup>, [Huwylar J](#)<sup>5</sup>, [Hattendorf J](#)<sup>6</sup>, [Keiser J](#)<sup>1,2</sup>.

#### BACKGROUND:

Schistosomiasis affects millions of people, yet treatment options are limited. The antimalarial Synriam (piperazine 150 mg/arterolane 750 mg) and the anthelmintic moxidectin revealed promising antischistosomal properties in preclinical or clinical studies.

#### METHODOLOGY:

We conducted two single-blind, randomized exploratory Phase 2 trials in *Schistosoma mansoni* and *S. haematobium*-infected adolescents in northern and central Côte d'Ivoire. Our primary endpoints were cure rates (CRs) and egg reduction rates (ERRs) based on geometric mean and safety. Each subject was asked to provide two stool samples (*S. mansoni* trial) for Kato-Katz analysis or three urine samples (*S. haematobium* trial) for urine filtration and one finger prick for malaria screening at baseline and follow-up. Participants were randomly assigned to either moxidectin, Synriam, Synriam plus praziquantel or praziquantel.

#### PRINCIPAL FINDINGS:

128 adolescents (age: 12-17 years) were included in each study. **Against *S. haematobium* moxidectin and Synriam revealed low efficacy. On the other hand, Synriam plus praziquantel and praziquantel yielded CRs of 60.0% and 38.5% and ERRs of 96.0% and 93.5%, respectively. CRs observed in the treatment of *S. mansoni* were 13.0%, 6.7%, 27.0%, and 27.6% for moxidectin, Synriam, Synriam plus praziquantel and praziquantel, respectively. ERRs ranged from 64.9% (Synriam) to 87.5% (praziquantel).**

#### CONCLUSION/SIGNIFICANCE:

Synriam and moxidectin show low efficacy against *S. haematobium*, hence an ancillary benefit is not expected when these drugs are used for treating onchocerciasis and malaria in co-endemic settings. Further studies are needed to corroborate our findings that moxidectin and Synriam show moderate ERRs against *S. mansoni*.

[Acta Trop.](#) 2016 Nov;163:142-8. doi: 10.1016/j.actatropica.2016.08.004. Epub 2016 Aug 3.

#### **Increasing the reach: Involving local Muslim religious teachers in a behavioral intervention to eliminate urogenital schistosomiasis in Zanzibar.**

[Celone M](#)<sup>1</sup>, [Person B](#)<sup>2</sup>, [Ali SM](#)<sup>3</sup>, [Lyimo JH](#)<sup>1</sup>, [Mohammed UA](#)<sup>1</sup>, [Khamis AN](#)<sup>1</sup>, [Mohammed YS](#)<sup>3</sup>, [Mohammed KA](#)<sup>1</sup>, [Rollinson D](#)<sup>4</sup>, [Knopp S](#)<sup>5</sup>.

#### Abstract

In Zanzibar, United Republic of Tanzania, Madrasa schools are influential institutions, where children and adults can learn about the interpretation of the Koran. We aimed to explore the involvement of Madrasa teachers for behavior change interventions in a randomized operational research trial designed to investigate the impact of multiple approaches to eliminate urogenital schistosomiasis transmission from Zanzibar. **Madrasa teachers performing in the 30 communities of the behavior change study arm were trained in new interactive and participatory teaching methods by the local behavioral team and provided with schistosomiasis-teaching tools for teaching about transmission and prevention in their Madrasa.** In July 2014, in a qualitative research study, we conducted 25 semi-structured interviews with Madrasa teachers to find out how they perceived their involvement in interventions against schistosomiasis. **In 2014, 5926 among the 8497 registered Madrasa students in 30 communities on Unguja and Pemba islands received health education and participated in interactive behavior change exercises about schistosomiasis.** Madrasa teachers reported that they valued their inclusion in the study and the opportunity to educate their students about schistosomiasis transmission, prevention, and treatment. They also perceived personal and community benefits as a result of their training and strongly supported the inclusion of additional Madrasa teachers in future intervention activities. Madrasa teachers



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are influential in the Zanzibari society, and hence are important change agents within our community-level behavioral intervention. They might constitute an untapped resource that can help to expand and increase acceptance of and participation in schistosomiasis and other neglected tropical disease control activities in African Muslim communities.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5019290/>

## School health and education

(See Adolescent health, Schistosomiasis)

[Psychol Health Med.](#) 2017 Apr;22(4):381-392. doi: 10.1080/13548506.2016.1153682. Epub 2016 Mar 10.

[A randomized-control trial for the teachers' diploma programme on psychosocial care, support and protection in Zambian government primary schools.](#)

[Kaljee L<sup>1</sup>](#), [Zhang L<sup>2</sup>](#), [Langhaug L<sup>3</sup>](#), [Munjile K<sup>4</sup>](#), [Tembo S<sup>5</sup>](#), [Menon A<sup>6</sup>](#), [Stanton B<sup>7</sup>](#), [Li X<sup>8</sup>](#), [Malungo J<sup>9</sup>](#).

### Abstract

Orphaned and vulnerable children (OVC) experience poverty, stigma, and abuse resulting in poor physical, emotional, and psychological outcomes. **The Teachers' Diploma Programme on Psychosocial Care, Support, and Protection is a child-centered 15-month long-distance learning program focused on providing teachers with the knowledge and skills to enhance their school environments, foster psychosocial support, and facilitate school-community relationships.** A randomized controlled trial was implemented in 2013-2014. Both teachers (n=325) and students (n=1378) were assessed at baseline and 15-months post-intervention from randomly assigned primary schools in Lusaka and Eastern Provinces, Zambia. Multilevel linear mixed models (MLM) indicate positive significant changes for intervention teachers on outcomes related to self-care, teaching resources, safety, social support, and gender equity. Positive outcomes for intervention students related to future orientation, respect, support, safety, sexual abuse, and bullying. Outcomes support the hypothesis that teachers and students benefit from a program designed to enhance teachers' psychosocial skills and knowledge.

## Skin and hair disease

## Surgical problems

[Paediatr Anaesth.](#) 2017 Aug;27(8):810-815. doi: 10.1111/pan.13179. Epub 2017 Jun 6.

[Effects of intraoperative liberal fluid therapy on postoperative nausea and vomiting in children-A randomized controlled trial.](#)

[Ashok V<sup>1</sup>](#), [Bala I<sup>1</sup>](#), [Bharti N<sup>1</sup>](#), [Jain D<sup>1</sup>](#), [Samujh R<sup>2</sup>](#).

### BACKGROUND:

Postoperative nausea and vomiting (PONV) is one of the most distressing complications following surgery. **Supplemental perioperative fluid therapy might be an effective strategy to reduce PONV in children.**

### OBJECTIVES:

**The study was conducted to evaluate the effects of intraoperative liberal fluid therapy with crystalloids on PONV in children.**



## METHODS:

In this randomized trial, a total of 150 children of 3-7 years undergoing lower abdominal and penile surgery under general anesthesia were randomly assigned into two groups. **"Restricted group" received 10 mL kg<sup>-1</sup> h<sup>-1</sup> and "Liberal group" received 30 mL kg<sup>-1</sup> h<sup>-1</sup> infusion of Ringer's lactate solution intraoperatively.** All patients received a caudal block and intravenous paracetamol for analgesia. No opioids and muscle relaxants were used. All episodes of nausea-vomiting and the requirement of rescue antiemetic were assessed during 24 hours postoperatively.

## RESULTS:

**The incidence of PONV was significantly less in the liberal group patients as compared to the restricted group; 33 (45.8%) patients in the restricted group had vomiting as compared to 20 (27.4%) patients in the liberal group (RR 0.59, 95% CI: 0.38-0.93, P=.021).**

The adjusted odds ratio of PONV for the liberal group vs restricted group was 2.24 (95% CI: 1.12-4.48, P=.022). The incidence of fluid intake during the first 6 postoperative hours was significantly higher in the restricted group patients; 60 (83%) children in the restricted group complained of thirst as compared to 12 (17%) children in the liberal group (RR 0.19, 95% CI: 0.18-0.33, P=.0001). The parents of the liberal group were more satisfied as compared to the restricted group (mean difference -0.9, 95% CI: -1.8, -0.1, P=.04). None of the children had any complication attributed to the liberal fluid therapy.

## CONCLUSION:

Liberal intraoperative fluid therapy was found to be effective in reducing PONV in children undergoing lower abdominal surgery.

[Pediatr Surg Int.](#) 2017 Feb;33(2):229-234. doi: 10.1007/s00383-016-4019-6. Epub 2016 Nov 10.

## [Role of nasogastric tube in children undergoing elective distal bowel surgery.](#)

[Khan NA](#)<sup>1</sup>, [Roy Choudhury S](#)<sup>2</sup>, [Yadav PS](#)<sup>1</sup>, [Prakash R](#)<sup>1</sup>, [Patel JN](#)<sup>1</sup>.

## BACKGROUND:

Nasogastric tubes are being routinely used in children and adults undergoing elective abdominal surgery without much scientific evidence supporting their true usefulness. The aim of our study was to assess the role of nasogastric tube in children undergoing elective distal bowel surgery.

## MATERIALS AND METHODS:

All pediatric patients undergoing elective distal bowel surgery were enrolled and randomized into two groups: those with nasogastric tube (NG group) or without nasogastric tube (NNG group). Outcome parameters such as resumption of bowel function, enteral feed tolerance, postoperative complications, hospital stay and patient with their parent satisfaction were compared between the groups.

## RESULTS:

A total of 60 patients were included with equal distribution in the NG and NNG groups. Patient variables were comparable in both the groups. **Patients in NNG group progressed to full oral feeds significantly earlier ( $57 \pm 18$  vs.  $106.07 \pm 18.35$  h,  $p < 0.001$ ) and had shorter duration of hospital stay ( $91.93 \pm 26.03$  vs.  $114.67 \pm 18.83$  h,  $p < 0.001$ ) as compared to the NG group.** Significant number of patients with nasogastric tube reported sore throat (9 vs. 1  $p = 0.03$ ) and nausea (5 vs. 0  $p = 0.010$ ). There was no significant difference in return of bowel function ( $39.43 \text{ h} \pm 15.92$  vs.  $43.60 \text{ h} \pm 17.77$ ,  $p = 0.171$ ), hiccups, sleep disturbance, complications and nasogastric tube reinsertion rate between the two groups.

## CONCLUSION:

**Routine use of nasogastric tube after elective distal bowel surgery in children is not necessary.**

[J Indian Assoc Pediatr Surg.](#) 2017 Apr-Jun;22(2):87-91. doi: 10.4103/jiaps.JIAPS\_228\_16.

**Primary Definitive Procedure versus Conventional Three-staged Procedure for the Management of Low-type Anorectal Malformation in Females: A Randomized Controlled Trial.**

[Gupta A](#)<sup>1</sup>, [Agarwala S](#)<sup>1</sup>, [Sreenivas V](#)<sup>2</sup>, [Srinivas M](#)<sup>1</sup>, [Bhatnagar V](#)<sup>1</sup>.

**INTRODUCTION:**

Females with Krickbeck low-type anorectal malformations - vestibular fistula (VF) and perineal fistula (PF) - are managed either by a primary definitive or conventional three-staged approach. Ultimate outcome in these children may be affected by wound dehiscence leading to healing by fibrosis. Most of the literature favors one approach over other based on retrospective analysis of their outcomes. Whether a statistically significant difference in wound dehiscence rates between these approaches exists needed to be seen.

**MATERIALS AND METHODS:**

A randomized controlled trial for girls <14 years with VF or PF was done. Random tables were used to randomize 33 children to Group I (primary procedure) and 31 to Group II (three-staged procedure). Statistical analysis was done for significance of difference ( $P < 0.05$ ) in the primary outcome (wound dehiscence) and secondary outcomes (immediate and early postoperative complications).

**RESULTS:**

Of the 64 children randomized, 54 (84%) had VF. Both groups were comparable in demography, clinical profile and age at surgery. The incidence of wound dehiscence (39.4% vs. 18.2%;  $P = 0.04$ ), immediate postoperative complications (51.5% vs. 12.9%;  $P = 0.001$ ), and early postoperative complications (42.4% vs. 12.9%;  $P = 0.01$ ) was significantly higher in Group I as compared to Group II. Six of 13 children (46.2%) with dehiscence in Group I required a diverting colostomy to be made.

**CONCLUSIONS:**

Females with VF or PF undergoing primary definitive procedure have a significantly higher incidence of wound dehiscence ( $P = 0.04$ ), immediate ( $P = 0.001$ ) and early postoperative complications ( $P = 0.01$ ).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5379879/>

[J Pediatr Surg.](#) 2016 Dec;51(12):2025-2029. doi: 10.1016/j.jpedsurg.2016.09.030. Epub 2016 Sep 15.

**Role of gabapentin and anticholinergics in management of neurogenic bladder after repair of spina bifida - a randomized controlled study.**

[Dash V](#)<sup>1</sup>, [Bawa M](#)<sup>2</sup>, [Mahajan JK](#)<sup>1</sup>, [Kanojia RP](#)<sup>1</sup>, [Samujh R](#)<sup>1</sup>, [Rao KL](#)<sup>1</sup>.

**BACKGROUND:**

Anticholinergics are well established in the management of neurogenic bladders. However, some patients do have sub-optimal response or severe side effects. This study is designed to assess and compare efficacy of gabapentin with oxybutynin in neurogenic bladders after surgery for spina bifida.

**METHODS:**

Patients were randomized into three groups after urodynamic studies and started on oxybutynin, gabapentin, and combination of both, respectively. Thorough clinical and urodynamic reassessment was done at 6 months and one year after starting treatment.

**RESULTS:**

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Forty-four patients (3-19years) were studied. Improvement was noted in symptoms as well as urodynamic parameters in all groups. Maximal improvement of symptom score was with combination of drugs at 1 year. In urodynamic studies, compliance, pressures, and capacity showed improvement, which was significant between the groups at both six months and 1 year for bladder pressures and volume. Improvement in compliance though marked was not statistically significant. Best response was seen in group receiving both drugs. Gabapentin was better tolerated than oxybutynin.

### CONCLUSION:

Gabapentin is a good alternative to oxybutynin for management of neurogenic bladder, both as monotherapy and as an add-on therapy. It has potential application in patients with inadequate response to anticholinergics.

[Asian Cardiovasc Thorac Ann.](#) 2017 Feb;25(2):118-122. doi: 10.1177/0218492316688416. Epub 2017 Jan 9.

### **Topical and low-dose intravenous tranexamic acid in cyanotic cardiac surgery.**

[Patel J<sup>1</sup>](#), [Prajapati M<sup>1</sup>](#), [Patel H<sup>2</sup>](#), [Gandhi H<sup>1</sup>](#), [Deodhar S<sup>1</sup>](#), [Pandya H<sup>3</sup>](#).

#### **Abstract**

**Background** Coagulopathy is a major problem in surgery for cyanotic congenital heart disease. Tranexamic acid has been used both topically and systemically and plays a vital role in pediatric cardiac surgery by reducing blood loss and blood product requirement. We aimed to determine the anti-fibrinolytic effectiveness of low-dose systemic or topical tranexamic acid or a combination of both.

**Methods** Seventy-five patients were divided in 3 groups of 25. Group A patients were given tranexamic acid 20 mg kg<sup>-1</sup> intravenously after sternotomy and 20 mg kg<sup>-1</sup> after heparin reversal. Group B patients were given tranexamic acid 50 mg kg<sup>-1</sup> in 20 mL of saline intrapericardially before sternal closure, with the drain clamped for 20 min. **Group C patients were given tranexamic acid 20 mg kg<sup>-1</sup> intravenously after sternotomy and 50 mg kg<sup>-1</sup>**

**intrapericardially before sternal closure.** A number of clinical variables were recorded in the first 3 postoperative days. Ventilator time, intensive care unit stay, and outcome were also recorded.

**Results** Chest tube drainage and blood product requirements were lowest in group C. Blood urea and serum creatinine levels were higher in groups A and C ( p < 0.05). Intensive care unit stay and ventilator time were similar in all 3 groups. No patient died and none had a seizure or other neurological event or thromboembolic complication postoperatively.

**Conclusion** **The combination of low-dose intravenous and topical tranexamic acid reduces postoperative blood loss and blood product requirement without incurring neurological, renal or thromboembolic complications. We recommend the routine use of topical and low-dose systemic tranexamic acid in cyanotic pediatric cardiac surgery.**

## Tuberculosis

(See also Vaccines: Tuberculosis vaccine)

[Lancet Infect Dis.](#) 2017 Apr;17(4):441-450. doi: 10.1016/S1473-3099(16)30384-X. Epub 2017 Jan 5.

### **Effect of new tuberculosis diagnostic technologies on community-based intensified case finding: a multicentre randomised controlled trial.**

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[Calligaro GL](#)<sup>1</sup>, [Zijenah LS](#)<sup>2</sup>, [Peter JG](#)<sup>3</sup>, [Theron G](#)<sup>4</sup>, [Buser V](#)<sup>5</sup>, [McNerney R](#)<sup>5</sup>, [Bara W](#)<sup>6</sup>, [Bandason T](#)<sup>7</sup>, [Govender U](#)<sup>5</sup>, [Tomasicchio M](#)<sup>5</sup>, [Smith L](#)<sup>5</sup>, [Mayosi BM](#)<sup>8</sup>, [Dhedha K](#)<sup>9</sup>.

### BACKGROUND:

Inadequate case detection results in high levels of undiagnosed tuberculosis in sub-Saharan Africa. Data for the effect of new diagnostic tools when used for community-based intensified case finding are not available, so we investigated whether the use of sputum Xpert-MTB/RIF and the Determine TB LAM urine test in two African communities could be effective.

### METHODS:

In a pragmatic, randomised, parallel-group trial with individual randomisation stratified by country, we compared sputum Xpert-MTB/RIF, and if HIV-infected, the Determine TB LAM urine test (novel diagnostic group), with laboratory-based sputum smear microscopy (routine diagnostic group) for intensified case finding in communities with high tuberculosis and HIV prevalence in Cape Town, South Africa, and Harare, Zimbabwe. Participants were randomly assigned (1:1) to these groups with computer-generated allocation lists, using culture as the reference standard. In Cape Town, participants were randomised and tested at an Xpert-equipped mobile van, while in Harare, participants were driven to a local clinic where the same diagnostic tests were done. The primary endpoint was the proportion of culture-positive tuberculosis cases initiating tuberculosis treatment in each study group at 60 days. This trial is registered at ClinicalTrials.gov, number [NCT01990274](#).

### FINDINGS:

Between Oct 18, 2013, and March 31, 2015, **2261 individuals were screened and 875 (39%) of these met the criteria for diagnostic testing. 439 participants were randomly assigned to the novel group and 436 to the routine group. 74 (9%) of 875 participants had confirmed tuberculosis.** If late culture-based treatment initiation was excluded, more patients with culture-positive tuberculosis were initiated on treatment in the novel group at 60 days (36 [86%] of 42 in the novel group vs 18 [56%] of 32 in the routine group). Thus the difference in the proportion initiating treatment between groups was 29% (95% CI 9-50,  $p=0.0047$ ) and 53% more patients initiated therapy in the novel diagnostic group than in the routine diagnostic group. One culture-positive patient was treated based only on a positive LAM test.

### INTERPRETATION:

**Compared with traditional tools, Xpert-MTB/RIF for community-based intensified case finding in HIV and tuberculosis-endemic settings increased the proportion of patients initiating treatment.** By contrast, urine LAM testing was not found to be useful for intensive case finding in this setting.

[Cochrane Database Syst Rev.](#) 2016 Nov 1;11:CD012163.

### Six-month therapy for abdominal tuberculosis.

[Jullien S](#)<sup>1</sup>, [Jain S](#), [Ryan H](#), [Ahuja V](#).

### BACKGROUND:

Tuberculosis (TB) of the gastrointestinal tract and any other organ within the abdominal cavity is abdominal TB, and most guidelines recommend the same six-month regimen used for pulmonary TB for people with this diagnosis. However, some physicians are concerned whether a six-month treatment regimen is long enough to prevent relapse of the disease, particularly in people with gastrointestinal TB, which may sometimes cause antituberculous drugs to be poorly absorbed. On the other hand, longer regimens are associated with poor adherence, which could increase relapse, contribute to drug resistance developing, and increase costs to patients and health providers.

### OBJECTIVES:

To compare six-month versus longer drug regimens to treat people that have abdominal TB.

### SEARCH METHODS:

We searched the following electronic databases up to 2 September 2016: the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase (accessed via OvidSP), LILACS, INDMED, and the South Asian Database of Controlled Clinical Trials. We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for ongoing trials. We also checked article reference lists.

### SELECTION CRITERIA:

We included randomized controlled trials (RCTs) that compared six-month regimens versus longer regimens that consisted of isoniazid, rifampicin, pyrazinamide, and ethambutol to treat adults and children that had abdominal TB. The primary outcomes were relapse, with a minimum of six-month follow-up after completion of antituberculous treatment (ATT), and clinical cure at the end of ATT.

### DATA COLLECTION AND ANALYSIS:

Two review authors independently selected trials, extracted data, and assessed the risk of bias in the included trials. For analysis of dichotomous outcomes, we used risk ratios (RR) with 95% confidence intervals (CIs). Where appropriate, we pooled data from the included trials in meta-analyses. We assessed the quality of the evidence using the GRADE approach.

### MAIN RESULTS:

We included three RCTs, with 328 participants, that compared six-month regimens with nine-month regimens to treat adults with intestinal and peritoneal TB. All trials were conducted in Asia, and excluded people with HIV, those with co-morbidities and those who had received ATT in the previous five years. Antituberculous regimens were based on isoniazid, rifampicin, pyrazinamide, and ethambutol, and these drugs were administered daily or thrice weekly under a directly observed therapy programme. The median duration of follow-up after completion of treatment was between 12 and 39 months. Relapse was uncommon, with two cases among 140 participants treated for six months, and no events among 129 participants treated for nine months. The small number of participants means we do not know whether or not there is a difference in risk of relapse between the two regimens (very low quality evidence). **At the end of therapy, there was probably no difference in the proportion of participants that achieved clinical cure between six-month and nine-month regimens (RR 1.02, 95% CI 0.97 to 1.08; 294 participants, 3 trials, moderate quality evidence). For death, there were 2/150 (1.3%) in the six-month group and 4/144 (2.8%) in the nine-month group.** All deaths occurred in the first four months of treatment, so was not linked to the duration of treatment in the included trials. Similarly, the number of participants that defaulted from treatment was small in both groups, and there may be no difference between them (RR 0.50, 95% CI 0.10 to 2.59; 294 participants, 3 trials, low quality evidence). Only one trial reported on adherence to treatment, with only one participant allocated to the nine-month regimen presenting poor adherence to treatment. We do not know whether six-month regimens are associated with fewer people experiencing adverse events that lead to treatment interruption (RR 0.53, 95% CI 0.18 to 1.55; 318 participants, 3 trials, very low quality evidence).

### AUTHORS' CONCLUSIONS:

**We found no evidence to suggest that six-month treatment regimens are inadequate for treating people that have intestinal and peritoneal TB, but numbers are small.** We did not find any incremental benefits of nine-month regimens regarding relapse at the end of follow-up, or clinical cure at the end of therapy, but our confidence in the relapse estimate is very low because of size of the trials. Further research is required to make confident conclusions regarding the safety of six-month treatment for people with abdominal TB. Larger studies that include HIV-positive people, with long follow-up for detecting relapse with reliability, would help improve our knowledge around this therapeutic question.

## Urinary tract infection

## Urology

## Vaccines and immunization

(see also deworming)

[World J Pediatr.](#) 2017 Jun;13(3):236-241. doi: 10.1007/s12519-017-0004-y. Epub 2017 Jan 19.  
**[Randomized controlled trial of topical EMLA and vapocoolant spray for reducing pain during wDPT vaccination.](#)**

[Gupta NK](#)<sup>1</sup>, [Upadhyay A](#)<sup>2</sup>, [Dwivedi AK](#)<sup>1</sup>, [Agarwal A](#)<sup>1</sup>, [Jaiswal V](#)<sup>1</sup>, [Singh A](#)<sup>1</sup>.

### BACKGROUND:

Intramuscular vaccination is among the most common source of iatrogenic pain in infants.

**Vapocoolant sprays are rapid-acting alternative to topical anesthetics. They provide transient anesthesia via evaporation induced skin cooling, and reduce pain due to vaccine injection in children and adults.** The objective was to compare the synergistic analgesic effect of eutectic mixture of local anesthetics (EMLA) with breastfeeding (EB group) and vapocoolant spray with breastfeeding (VB group) to that of only breastfeeding (BO group) during whole cell diphtheria, pertussis and tetanus (wDPT) vaccination.

### METHODS:

A double blind randomized controlled trial was done to include infants up to 3 months of age who came for their first wDPT vaccination. The primary outcome variable was the duration of cry after vaccination. Secondary outcome variables were Modified Facial Coding Score, Neonatal Infant Pain Scale and latency of onset of cry.

### RESULTS:

Of the 201 eligible participants, 111 babies were excluded and remaining 90 babies were randomized into three groups of thirty each. The groups did not differ significantly in baseline characteristics. **Median (interquartile range, IQR) of duration of cry was lesser [35.86 (21.07-107.75) seconds] in babies receiving EMLA cream with breast feeding (EB group) and in babies receiving vapocoolant spray with breast feeding (VB group) [32.58 (21.25-106.21) seconds] as compared to babies receiving only breast feeding (BO group) [67.5 (27.6-180) seconds] (P=0.147).** Difference in median (IQR) of latency of cry was not statistically significant. Modified Facial Coding Score and Neonatal Infant Pain Scale at 1 minute and 3 minutes was significantly lower in the EB and VB group, as compared to the BO group (P<0.05).

### CONCLUSION:

Addition of topical EMLA application or vapocoolant spray to breastfeeding during wDPT vaccination does not reduce duration of cry in infants up to 3 months of age. However, they are able to show reduction in pain score and further studies are warranted to assess their efficacy as pain relief measures in infants and children.



BCG vaccine

Cholera vaccine

Dengue vaccine

[Lancet Infect Dis](#). 2017 Jun;17(6):615-625. doi: 10.1016/S1473-3099(17)30166-4. Epub 2017 Mar 30.

**Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study.**

[Sáez-Llorens X](#)<sup>1</sup>, [Tricou V](#)<sup>2</sup>, [Yu D](#)<sup>3</sup>, [Rivera L](#)<sup>4</sup>, [Tuboi S](#)<sup>5</sup>, [Garbes P](#)<sup>6</sup>, [Borkowski A](#)<sup>7</sup>, [Wallace D](#)<sup>7</sup>.

**BACKGROUND:**

Dengue is the most common mosquito-borne viral disease in human beings, and vector control has not halted its spread worldwide. A dengue vaccine for individuals aged 9 years and older has been licensed, but there remains urgent medical need for a vaccine that is safe and effective against all four dengue virus serotypes (DENV-1-4) in recipients of all ages. Here, we present **the preplanned interim analyses at 6 months of a tetravalent dengue vaccine candidate (TDV)**, which is comprised of an attenuated DENV-2 virus strain (TDV-2) and three chimeric viruses containing the premembrane and envelope protein genes of DENV-1, DENV-3, and DENV-4 genetically engineered into the attenuated TDV-2 genome backbone (TDV-1, TDV-3, and TDV-4).

**METHODS:**

An ongoing phase 2, randomised, double-blind, placebo-controlled trial of a TDV is being done at three sites in dengue-endemic countries (Dominican Republic, Panama, and the Philippines) to determine its safety and immunogenicity over 48 months in healthy participants aged 2-17 years who were **randomly assigned (1:2:5:1) using an interactive web response system (stratified by age) to subcutaneous TDV injection (one 0.5 mL dose containing  $2.5 \times 10^4$  plaque-forming units [PFU] of TDV-1;  $6.3 \times 10^3$  PFU of TDV-2;  $3.2 \times 10^4$  PFU of TDV-3; and  $4.0 \times 10^5$  PFU of TDV-4) in different dose schedules (two-dose regimen at 0 and 3 months, one dose at 0 months, or one dose at 0 months and a booster at 12 months) or placebo. The primary endpoint of this 6 month interim analysis was geometric mean titres (GMTs) of neutralising antibodies against DENV-1-4 in the per-protocol immunogenicity subset at 1 month, 3 months, and 6 months after the first injection.** Safety was assessed as a secondary outcome as percentage of participants with serious adverse events in all participants who were injected (safety set), and solicited and unsolicited adverse events (immunogenicity subset). This trial is registered with ClinicalTrials.gov, number [NCT02302066](#).

**FINDINGS:**

1800 participants were enrolled between Dec 5, 2014, and Feb 13, 2015. 1794 participants were given study injection as follows: 200 participants were given two-dose regimen at 0 and 3 months (group 1), 398 were given one dose at 0 months (group 2), 998 were given one dose at 0 months and will be given (trial ongoing) a booster at 12 months (group 3), and 198 were given placebo (group 4). These 1794 participants were included in the safety set; **562 participants were randomly assigned to the immunogenicity subset**, of which 503 were included in the per-protocol set. **TDV elicited neutralising antibodies against all DENV serotypes, which peaked at 1 month and remained elevated above baseline at 6 months.** At 6 months, GMTs of neutralising antibodies against DENV-1 were 489 (95% CI 321-746) for group 1, 434 (306-615) for group 2, 532 (384-738) for group 3, and 62 (32-120) for group 4; GMTs of neutralising antibodies against DENV-2 were 1565 (1145-2140) for group 1, 1639 (1286-2088) for group 2,

1288 (1031-1610) for group 3, and 86 (44-169) for group 4; GMTs of neutralising antibodies against DENV-3 were 160 (104-248) for group 1, 151 (106-214) for group 2, 173 (124-240) for group 3, and 40 (23-71) for group 4; and GMTs of neutralising antibodies against DENV-4 were 117 (79-175) for group 1, 110 (80-149) for group 2, 93 (69-125) for group 3, and 24 (15-38) for group 4. No vaccine-related serious adverse events occurred; 15 (3%) of 562 participants in the immunogenicity subset reported vaccine-related unsolicited adverse events. The reactogenicity profile of TDV was acceptable, and similar to previous findings with TDV.

### INTERPRETATION:

TDV is safe and immunogenic in individuals aged 2-17 years, irrespective of previous dengue exposure. A second TDV dose induced enhanced immunogenicity against DENV-3 and DENV-4 in children who were seronegative before vaccination. These data supported the initiation of phase 3 evaluation of the efficacy and safety of TDV given in a two-dose schedule 3 months apart, with analyses that take into account baseline age and dengue serostatus.

[PLoS Negl Trop Dis](https://doi.org/10.1371/journal.pntd.0004821). 2016 Jul 14;10(7):e0004821. doi: 10.1371/journal.pntd.0004821.

eCollection 2016 Jul.

### Safety Overview of a Recombinant Live-Attenuated Tetravalent Dengue Vaccine: Pooled Analysis of Data from 18 Clinical Trials.

[Gailhardou S](#)<sup>1</sup>, [Skipetrova A](#)<sup>1</sup>, [Dayan GH](#)<sup>2</sup>, [Jezorwski J](#)<sup>2</sup>, [Saville M](#)<sup>1</sup>, [Van der Vliet D](#)<sup>3</sup>, [Wartel TA](#)<sup>4</sup>.

#### Abstract

A recombinant live attenuated tetravalent dengue vaccine (CYD-TDV) has been shown to be efficacious in preventing virologically-confirmed dengue disease, severe dengue disease and dengue hospitalization in children aged 2-16 years in Asia and Latin America. We analyzed pooled safety data from 18 phase I, II and III clinical trials in which the dengue vaccine was administered to participants aged 2-60 years, including long-term safety follow-up in three efficacy trials. The participants were analyzed according to their age at enrollment. The percentage of participants aged 2-60 years reporting  $\geq 1$  solicited injection-site or systemic reactions was slightly higher in the CYD-TDV group than in the placebo group. The most common solicited injection-site reactions were pain. Headache and malaise were the most common solicited systemic reactions. In both groups 0.3% of participants discontinued for safety reasons. The most common unsolicited adverse events were injection-site reactions, gastrointestinal disorders, and infections. Reactogenicity did not increase with successive doses of CYD-TDV. The frequency and nature of SAEs occurring within 28 days of any dose were similar in the CYD-TDV and placebo groups and were common medical conditions that could be expected as a function of age. Baseline dengue virus serostatus did not appear to influence the safety profile. No vaccine-related anaphylactic reactions, neurotropic events or viscerotropic events were reported. In year 3 after dose 1, an imbalance for dengue hospitalization, including for severe dengue, observed in participants aged  $<9$  years in the CYD-TDV group compared with the placebo group was not observed for participants aged  $\geq 9$  years. In Year 4, this imbalance in participants aged  $<9$  years was less marked, giving an overall lower risk of dengue hospitalization or severe dengue from dose 1 to Year 4 in the CYD-TDV group. These results have contributed to the definition of the target population for vaccination ( $\geq 9$  years old) for which CYD-TDV has a satisfactory safety profile. Long-term safety will continue to be monitored in the ongoing follow-up of efficacy trials. Safety and effectiveness in real-life settings will be assessed through post-licensure studies.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4945086/>

## Enterovirus 71 vaccine

[J Infect Dis.](#) 2017 Jan 1;215(1):56-63. doi: 10.1093/infdis/jiw502. Epub 2016 Oct 17.

### **2-Year Efficacy, Immunogenicity, and Safety of Vigoo Enterovirus 71 Vaccine in Healthy Chinese Children: A Randomized Open-Label Study.**

[Wei M](#)<sup>1</sup>, [Meng F](#)<sup>2</sup>, [Wang S](#)<sup>3</sup>, [Li J](#)<sup>2</sup>, [Zhang Y](#)<sup>4</sup>, [Mao Q](#)<sup>5</sup>, [Hu Y](#)<sup>2</sup>, [Liu P](#)<sup>3</sup>, [Shi N](#)<sup>6</sup>, [Tao H](#)<sup>2</sup>, [Chu K](#)<sup>2</sup>, [Wang Y](#)<sup>3</sup>, [Liang Z](#)<sup>5</sup>, [Li X](#)<sup>4</sup>, [Zhu F](#)<sup>1,2</sup>.

#### **BACKGROUND:**

This study evaluated the 2-year efficacy, immunogenicity, and safety of the Vigoo enterovirus 71 (EV71) vaccine.

#### **METHOD:**

In an initial phase 3 study, we randomly assigned healthy infants and children aged 6-35 months (ratio, 1:1) to receive 2 doses of either EV71 vaccine (5120 participants) or placebo (5125 participants) at days 0 and 28, and followed them for 12 months after vaccination. In this extended follow-up study, we continued to evaluate the efficacy, immunogenicity, and safety of the EV71 vaccine for up to 2 years.

#### **RESULTS:**

Overall efficacy was 94.84% (95% confidence interval [CI], 83.53%-98.38%) during the 2-year follow-up period ( $P < .0001$ ), and the vaccine efficacy during the second year was 100.00% (95% CI, 84.15%-100.00%) against EV71-associated hand-foot-and-mouth disease (HFMD;  $P < .0001$ ). Geometric mean titers of neutralizing antibody in participants remained high during the 2-year follow-up period, and no vaccine-related serious adverse events were recorded.

#### **CONCLUSIONS:**

Two doses of Vigoo EV71 vaccine could provide sustained protection against EV71-associated HFMD in healthy Chinese children.

## Hepatitis A vaccine

[Clin Microbiol Infect.](#) 2016 Sep;22(9):811.e9-811.e15. doi: 10.1016/j.cmi.2016.06.004. Epub 2016 Jun 23.

### **Comparison of the safety and immunogenicity of live attenuated and inactivated hepatitis A vaccine in healthy Chinese children aged 18 months to 16 years: results from a randomized, parallel controlled, phase IV study.**

[Ma F](#)<sup>1</sup>, [Yang J](#)<sup>2</sup>, [Kang G](#)<sup>3</sup>, [Sun Q](#)<sup>2</sup>, [Lu P](#)<sup>1</sup>, [Zhao Y](#)<sup>2</sup>, [Wang Z](#)<sup>1</sup>, [Luo J](#)<sup>2</sup>, [Wang Z](#)<sup>4</sup>.

#### **Abstract**

For large-scale immunization of children with hepatitis A (HA) vaccines in China, accurately designed studies comparing the safety and immunogenicity of the live attenuated HA vaccine (HA-L) and inactivated HA vaccine (HA-I) are necessary. A randomized, parallel controlled, phase IV clinical trial was conducted with 6000 healthy children aged 18 months to 16 years. HA-L or HA-I was administered at a ratio of 1: 1 to randomized selected participants. The safety and immunogenicity were evaluated. Both HA-L and HA-I were well tolerated by all participants. **The immunogenicity results showed that the seroconversion rates (HA-L versus HA-I: 98.0% versus 100%, respectively,  $p > 0.05$ ), and geometric mean concentrations in participants negative for antibodies against HA virus IgG (anti-HAV IgG) before vaccination did not differ significantly between the two types of vaccines (HA-L versus HA-I first dose: 898.9 versus 886.2 mIU/mL, respectively,  $p > 0.05$ ). After**

administration of the booster dose of HA-I, the geometric mean concentrations of anti-HAV IgG (HA-I booster dose: 2591.2 mIU/mL) was higher than that after the first dose ( $p < 0.05$ ) and that reported in participants administered HA-L ( $p < 0.05$ ). Additionally, 12 (25%) of the 48 randomized selected participants who received HA-L tested positive for HA antigen in stool samples. Hence, both HA-L and HA-I could provide acceptable immunogenicity in children. The effects of long-term immunogenicity after natural exposure to wild-type HA virus and the possibility of mutational shifts of the live vaccine virus in the field need to be studied in more detail.

### Hepatitis B vaccine

[Pediatr Infect Dis J.](#) 2017 Jan;36(1):94-101.

#### **Comparative Efficacy, Safety and Immunogenicity of Hepavax-Gene TF and Engerix-B Recombinant Hepatitis B Vaccines in Neonates in China.**

[Zhu F<sup>1</sup>](#), [Deckx H](#), [Roten R](#), [Michiels B](#), [Sarnecki M](#).

#### **BACKGROUND:**

The aim of the study was to compare efficacy, immunogenicity and safety of Hepavax-Gene TF (thimerosal-free) vaccine with comparator in Chinese neonates.

#### **METHODS:**

A double-blind, randomized, parallel-group, stratified study was conducted at multiple sites in China in healthy neonates, consisting of 3 doses of Hepavax-Gene TF or Engerix-B vaccines administered at birth, 1 and 6 months of age, with a 6-month follow-up after vaccination. On the basis of hepatitis B virus (HBV) infection status of mothers, infants were assigned to one of 2 study strata for mothers positive for HBV infection (stratum 1), with or without active replicating virus (substrata 1a, 1b), and for HBV negative mothers (stratum 2).

#### **RESULTS:**

Mother-to-child HBV transmission was prevented in >95% of neonates immunized with Hepavax-Gene TF in stratum 1 at all timepoints and was noninferior to Engerix-B. Seroprotection rates (anti-HBs antibody  $\geq 10$  IU/L) at 1 and 6 months postvaccination for Hepavax-Gene TF were over 90% for all exposed neonates. Immunogenicity of Hepavax-Gene was noninferior to Engerix-B except for neonates in substratum 1a at 12 months. Geometric mean concentrations between vaccine groups were not significantly different for neonates at all timepoints except in substratum 1b at 7 months. Both vaccines were well tolerated and had similar local and systemic adverse event profiles.

#### **CONCLUSIONS:**

Hepavax-Gene TF vaccine was equally effective and noninferior to Engerix-B in terms of prevention of mother-to-child HBV transmission in neonates born to mothers positive for hepatitis B surface antigen. Both vaccines elicited seroprotective levels in >90% of all exposed neonates at 12-month follow-up. Both vaccines were well tolerated with similar adverse event profiles.

[Pediatr Infect Dis J.](#) 2017 May;36(5):e157-e161. doi: 10.1097/INF.0000000000001535.

#### **A Randomized Controlled Trial to Evaluate a Potential Hepatitis B Booster Vaccination Strategy Using Combined Hepatitis A and B Vaccine.**

[Li F<sup>1</sup>](#), [Hu Y](#), [Zhou Y](#), [Chen L](#), [Xia W](#), [Song Y](#), [Tan Z](#), [Gao L](#), [Yang Z](#), [Zeng G](#), [Han X](#), [Li J](#), [Li J](#).

#### **BACKGROUND:**

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Booster doses could play a major role in no responders or low responders to primary hepatitis B (HB) vaccine. Planned time point for hepatitis A vaccination in China provides a good opportunity to carry out HB booster dose by using combined hepatitis A and B vaccine.

### METHODS:

A randomized, double-blinded clinical trial was conducted to compare the immunogenicity and safety of toddlers 18-24 months of age receiving 3 different vaccination regimens: 2 doses of inactivated hepatitis A vaccine (group 1), 1 dose of inactivated hepatitis A vaccine plus 1 dose of combined hepatitis A and B vaccine (group 2) or 2 doses of combined hepatitis A and B vaccine (group 3).

### RESULTS:

All 3 groups showed 100% seroprotection for antihepatitis A virus antibody after vaccination. Seroprotection rate for anti-HB antibody before vaccination ranged from 79.5% to 92.9% in the 3 groups. After second inoculation, anti-HBs seroprotection increased from 92.9% to 100% in group 2 with postvaccination geometric mean concentration (GMC) of 2258.3 mIU/mL and from 79.5% to 98.9% in group 3 with postvaccination GMC of 2055.3 mIU/mL. The adverse events were not statistically different among groups ( $P = 0.345$ ).

### CONCLUSIONS:

Combined hepatitis A and B vaccine could stimulate high level of both antihepatitis A virus and anti-HBs antibodies and not increase adverse events, providing a new choice for HB booster.

## HIV vaccine

## HPV vaccine

[J Natl Cancer Inst.](#) 2017 Jan 28;109(7). pii: djw300. doi: 10.1093/jnci/djw300. Print 2017 Jan.

### Evaluation of Type Replacement Following HPV16/18 Vaccination: Pooled Analysis of Two Randomized Trials.

[Tota JE<sup>1</sup>](#), [Struyf F<sup>2</sup>](#), [Merikukka M<sup>2</sup>](#), [Gonzalez P<sup>2</sup>](#), [Kreimer AR<sup>2</sup>](#), [Bi D<sup>2</sup>](#), [Castellsagué X<sup>2</sup>](#), [de Carvalho NS<sup>2</sup>](#), [Garland SM<sup>2</sup>](#), [Harper DM<sup>2</sup>](#), [Karkada N<sup>2</sup>](#), [Peters K<sup>2</sup>](#), [Pope WA<sup>2</sup>](#), [Porrás C<sup>2</sup>](#), [Quint W<sup>2</sup>](#), [Rodriguez AC<sup>2</sup>](#), [Schiffman M<sup>2</sup>](#), [Schussler J<sup>2</sup>](#), [Skinner SR<sup>2</sup>](#), [Teixeira JC<sup>2</sup>](#), [Hildesheim A<sup>2</sup>](#), [Lehtinen M<sup>2</sup>](#); [Costa Rica Vaccine Trial and the PATRICIA study groups.](#)

### BACKGROUND:

Current HPV vaccines do not protect against all oncogenic HPV types. Following vaccination, type replacement may occur, especially if different HPV types competitively interact during natural infection. Because of their common route of transmission, it is difficult to assess type interactions in observational studies. Our aim was to evaluate type replacement in the setting of HPV vaccine randomized controlled trials (RCTs).

### METHODS:

Data were pooled from the Costa Rica Vaccine Trial (CVT; [NCT00128661](#)) and PATRICIA trial ([NCT001226810](#))-two large-scale, double-blind RCTs of the HPV-16/18 AS04-adjuvanted vaccine-to compare cumulative incidence of nonprotected HPV infections across trial arms after four years. Negative rate difference estimates (rate in control minus vaccine arm) were interpreted as evidence of replacement if the associated 95% confidence interval excluded zero. All statistical tests were two-sided.

### RESULTS:

After applying relevant exclusion criteria, 21 596 women were included in our analysis (HPV arm = 10 750; control arm = 10 846). Incidence rates (per 1000 infection-years) were lower in the HPV arm than in the control arm for grouped nonprotected oncogenic types (rate difference



= 1.6, 95% confidence interval [CI] = 0.9 to 2.3) and oncogenic/nononcogenic types (rate difference = 0.2, 95% CI = -0.3 to 0.7). Focusing on individual HPV types separately, no deleterious effect was observed. In contrast, a statistically significant protective effect (positive rate difference and 95% CI excluded zero) was observed against oncogenic HPV types 35, 52, 58, and 68/73, as well as nononcogenic types 6 and 70.

### CONCLUSION:

**HPV type replacement does not occur among vaccinated individuals within four years and is unlikely to occur in vaccinated populations.**

[JAMA](#). 2016 Dec 13;316(22):2411-2421. doi: 10.1001/jama.2016.17615.

### **Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women.**

[Iversen OE](#)<sup>1</sup>, [Miranda MJ](#)<sup>2</sup>, [Ulled A](#)<sup>3</sup>, [Soerdal T](#)<sup>4</sup>, [Lazarus E](#)<sup>5</sup>, [Chokephaibulkit K](#)<sup>6</sup>, [Block SL](#)<sup>7</sup>, [Skrivanek A](#)<sup>8</sup>, [Nur Azurah AG](#)<sup>9</sup>, [Fong SM](#)<sup>10</sup>, [Dvorak V](#)<sup>11</sup>, [Kim KH](#)<sup>12</sup>, [Cestero RM](#)<sup>13</sup>, [Berkovitch M](#)<sup>14</sup>, [Ceyhan M](#)<sup>15</sup>, [Ellison MC](#)<sup>16</sup>, [Ritter MA](#)<sup>16</sup>, [Yuan SS](#)<sup>16</sup>, [DiNubile MJ](#)<sup>16</sup>, [Saah AJ](#)<sup>16</sup>, [Luxembourg A](#)<sup>16</sup>.

### **Importance:**

Human papillomavirus (HPV) infections cause anogenital cancers and warts. The 9-valent HPV vaccine provides protection against 7 high-risk types of HPV responsible for 90% of cervical cancers and 2 other HPV types accounting for 90% of genital warts.

### **Objective:**

To determine whether HPV type-specific antibody responses would be noninferior among girls and boys aged 9 to 14 years after receiving 2 doses of the 9-valent HPV vaccine compared with adolescent girls and young women aged 16 to 26 years receiving 3 doses.

### **Design, Setting, and Participants:**

Open-label, noninferiority, immunogenicity trial conducted at 52 ambulatory care sites in 15 countries. The study was initiated on December 16, 2013, with the last participant visit for this report on June 19, 2015. Five cohorts were enrolled: (1) girls aged 9 to 14 years to receive 2 doses 6 months apart (n = 301); (2) boys aged 9 to 14 years to receive 2 doses 6 months apart (n = 301); (3) girls and boys aged 9 to 14 years to receive 2 doses 12 months apart (n = 301); (4) girls aged 9 to 14 years to receive 3 doses over 6 months (n = 301); and (5) a control group of adolescent girls and young women aged 16 to 26 years to receive 3 doses over 6 months (n = 314).

### **Interventions:**

Two doses of the 9-valent HPV vaccine administered 6 or 12 months apart or 3 doses administered over 6 months.

### **Main Outcomes and Measures:**

The primary end point was prespecified as the antibody response against each HPV type assessed 1 month after the last dose using a competitive immunoassay. Each of the three 2-dose regimens was compared with the standard 3-dose schedule in adolescent girls and young women using a noninferiority margin of 0.67 for the ratio of the antibody geometric mean titers.

### **Results:**

Of the 1518 participants (753 girls [mean age, 11.4 years]; 451 boys [mean age, 11.5 years]; and 314 adolescent girls and young women [mean age, 21.0 years]), 1474 completed the study and data from 1377 were analyzed. At 4 weeks after the last dose, HPV antibody responses in girls and boys given 2 doses were noninferior to HPV antibody responses in adolescent girls and young women given 3 doses ( $P < .001$  for each HPV type). Compared with adolescent girls and young women who received 3 doses over 6 months, the 1-sided 97.5% CIs for the ratio of HPV antibody geometric mean titers at 1 month after the last dose across the 9 HPV subtypes ranged



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from 1.36 to  $\infty$  to 2.50 to  $\infty$  for girls who received 2 doses 6 months apart; from 1.37 to  $\infty$  to 2.55 to  $\infty$  for boys who received 2 doses 6 months apart; and from 1.61 to  $\infty$  to 5.36 to  $\infty$  for girls and boys who received 2 doses 12 months apart.

### Conclusions and Relevance:

**Among girls and boys aged 9 to 14 years receiving 2-dose regimens of a 9-valent HPV vaccine separated by 6 or 12 months, immunogenicity 4 weeks after the last dose was noninferior to a 3-dose regimen in a cohort of adolescent girls and young women.** Further research is needed to assess persistence of antibody responses and effects on clinical outcomes.

Free access: <http://jamanetwork.com/journals/jama/fullarticle/2588254>

[J Infect Dis](#). 2016 Aug 15;214(4):525-36. doi: 10.1093/infdis/jiw036. Epub 2016 Feb 3.

### Randomized Open Trial Comparing 2-Dose Regimens of the Human Papillomavirus 16/18 AS04-Adjuvanted Vaccine in Girls Aged 9-14 Years Versus a 3-Dose Regimen in Women Aged 15-25 Years.

[Puthanakit T](#)<sup>1</sup>, [Huang LM](#)<sup>2</sup>, [Chiu CH](#)<sup>3</sup>, [Tang RB](#)<sup>4</sup>, [Schwarz TF](#)<sup>5</sup>, [Esposito S](#)<sup>6</sup>, [Frenette L](#)<sup>7</sup>, [Giaquinto C](#)<sup>8</sup>, [McNeil S](#)<sup>9</sup>, [Rheault P](#)<sup>10</sup>, [Durando P](#)<sup>11</sup>, [Horn M](#)<sup>12</sup>, [Klar M](#)<sup>13</sup>, [Poncelet S](#)<sup>14</sup>, [De Simoni S](#)<sup>14</sup>, [Friel D](#)<sup>15</sup>, [De Muynck B](#)<sup>15</sup>, [Suryakiran PV](#)<sup>16</sup>, [Hezareh M](#)<sup>17</sup>, [Descamps D](#)<sup>15</sup>, [Thomas F](#)<sup>15</sup>, [Struyf F](#)<sup>15</sup>.

### BACKGROUND:

This randomized, open trial compared regimens including 2 doses (2D) of human papillomavirus (HPV) 16/18 AS04-adjuvanted vaccine in girls aged 9-14 years with one including 3 doses (3D) in women aged 15-25 years.

### METHODS:

Girls aged 9-14 years were randomized to receive 2D at months 0 and 6 (M0,6; (n = 550) or months 0 and 12 (M0,12; n = 415), and women aged 15-25 years received 3D at months 0, 1, and 6 (n = 482). End points included noninferiority of HPV-16/18 antibodies by enzyme-linked immunosorbent assay for 2D (M0,6) versus 3D (primary), 2D (M0,12) versus 3D, and 2D (M0,6) versus 2D (M0,12); neutralizing antibodies; cell-mediated immunity; reactogenicity; and safety. Limits of noninferiority were predefined as <5% difference in seroconversion rate and <2-fold difference in geometric mean antibody titer ratio.

### RESULTS:

One month after the last dose, both 2D regimens in girls aged 9-14 years were noninferior to 3D in women aged 15-25 years and 2D (M0,12) was noninferior to 2D (M0,6). Geometric mean antibody titer ratios (3D/2D) for HPV-16 and HPV-18 were 1.09 (95% confidence interval, .97-1.22) and 0.85 (.76-.95) for 2D (M0,6) versus 3D and 0.89 (.79-1.01) and 0.75 (.67-.85) for 2D (M0,12) versus 3D. The safety profile was clinically acceptable in all groups.

### CONCLUSIONS:

**The 2D regimens for the HPV-16/18 AS04-adjuvanted vaccine in girls aged 9-14 years (M0,6 or M0,12) elicited HPV-16/18 immune responses that were noninferior to 3D in women aged 15-25 years.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4957434/>

Influenza vaccine

[Lancet Infect Dis.](#) 2016 Sep;16(9):1026-35. doi: 10.1016/S1473-3099(16)30054-8. Epub 2016 May 31.

**Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial.**

[Tapia MD](#)<sup>1</sup>, [Sow SO](#)<sup>2</sup>, [Tamboura B](#)<sup>2</sup>, [Tégueté I](#)<sup>3</sup>, [Pasetti MF](#)<sup>1</sup>, [Kodio M](#)<sup>2</sup>, [Onwuchekwa U](#)<sup>2</sup>, [Tennant SM](#)<sup>1</sup>, [Blackwelder WC](#)<sup>1</sup>, [Coulibaly F](#)<sup>2</sup>, [Traoré A](#)<sup>2</sup>, [Keita AM](#)<sup>2</sup>, [Haidara FC](#)<sup>2</sup>, [Diallo F](#)<sup>2</sup>, [Doumbia M](#)<sup>2</sup>, [Sanogo D](#)<sup>2</sup>, [DeMatt E](#)<sup>4</sup>, [Schluterma NH](#)<sup>5</sup>, [Buchwald A](#)<sup>5</sup>, [Kotloff KL](#)<sup>1</sup>, [Chen WH](#)<sup>1</sup>, [Orenstein EW](#)<sup>6</sup>, [Orenstein LA](#)<sup>7</sup>, [Villanueva J](#)<sup>8</sup>, [Bresee J](#)<sup>8</sup>, [Treanor J](#)<sup>9</sup>, [Levine MM](#)<sup>10</sup>.

**BACKGROUND:**

Despite the heightened risk of serious influenza during infancy, vaccination is not recommended in infants younger than 6 months. **We aimed to assess the safety, immunogenicity, and efficacy of maternal immunisation with trivalent inactivated influenza vaccine for protection of infants against a first episode of laboratory-confirmed influenza.**

**METHODS:**

We did this prospective, active-controlled, observer-blind, randomised phase 4 trial at six referral centres and community health centres in Bamako, Mali. **Third-trimester pregnant women (≥28 weeks' gestation) were randomly assigned (1:1), via a computer-generated, centre-specific list with alternate block sizes of six or 12, to receive either trivalent inactivated influenza vaccine or quadrivalent meningococcal vaccine.** Study personnel administering vaccines were not masked to treatment allocation, but allocation was concealed from clinicians, laboratory personnel, and participants. **Infants were visited weekly until age 6 months to detect influenza-like illness; laboratory-confirmed influenza diagnosed with RT-PCR.** We assessed **two coprimary objectives: vaccine efficacy against laboratory-confirmed influenza in infants born to women immunised any time prepartum (intention-to-treat population), and vaccine efficacy in infants born to women immunised at least 14 days prepartum (per-protocol population).** The primary outcome was the occurrence of a first case of laboratory-confirmed influenza by age 6 months. This trial is registered with ClinicalTrials.gov, number [NCT01430689](#).

**FINDINGS:**

We did this trial from Sept 12, 2011, to Jan 28, 2014. Between Sept 12, 2011, and April 18, 2013, **we randomly assigned 4193 women to receive trivalent inactivated influenza vaccine (n=2108) or quadrivalent meningococcal vaccine (n=2085).** There were 4105 livebirths; 1797 (87%) of 2064 infants in the trivalent inactivated influenza vaccine group and 1793 (88%) of 2041 infants in the quadrivalent meningococcal vaccine group were followed up until age 6 months. We recorded 5279 influenza-like illness episodes in 2789 (68%) infants, of which **131 (2%) episodes were laboratory-confirmed influenza. 129 (98%) cases of laboratory-confirmed influenza were first episodes (n=77 in the quadrivalent meningococcal vaccine group vs n=52 in the trivalent inactivated influenza vaccine group).** In the intention-to-treat population, overall infant vaccine efficacy was 33·1% (95% CI 3·7-53·9); in the per-protocol population, vaccine efficacy was 37·3% (7·6-57·8). Vaccine efficacy remained robust during the first 4 months of follow-up (67·9% [95% CI 35·1-85·3] by intention to treat and 70·2% [35·7-87·6] by per protocol), before diminishing during the fifth month (57·3% [30·6-74·4] and 60·7 [33·8-77·5], respectively). Adverse event rates in women and infants were similar among groups. Pain at the injection site was more common in women given quadrivalent meningococcal vaccine than in those given trivalent inactivated influenza vaccine (n=253 vs n=132; p<0·0001), although 354 [92%] reactions were mild. Obstetrical and non-obstetrical serious adverse events were reported in 60 (3%) women in the quadrivalent meningococcal vaccine group and 61 (3%) women in the trivalent inactivated influenza vaccine group. **Presumed neonatal infection was more common in infants in the trivalent inactivated**

**influenza vaccine group than in those in the quadrivalent meningococcal vaccine group (n=60 vs n=37; p=0.02).** No serious adverse events were related to vaccination.

**INTERPRETATION:**

Vaccination of pregnant women with trivalent inactivated influenza vaccine in Mali-a poorly resourced country with high infant mortality-was technically and logistically feasible and protected infants from laboratory-confirmed influenza for 4 months. With adequate financing to procure the vaccine, implementation will parallel the access to antenatal care and immunisation coverage of pregnant women with tetanus toxoid.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4985566/>

**Comment**

*It is good news that maternal immunization with influenza vaccine provides some protection against influenza in infants in the first 6 months of life. It is difficult to understand how vaccine efficacy could be reported to be as high as 60-70% in the first 4 months, and 50-60% in the fifth month, when overall vaccine efficacy in first 6 months was only 33-37%. There is no comment in the discussion on the possible reasons for the higher risk of presumed neonatal infection in the influenza vaccinated group, but this is an unexpected adverse finding that may have occurred by chance, but should be investigated.*

**Japanese encephalitis virus vaccine**

[Pediatr Infect Dis J.](#) 2017 Apr;36(4):e108-e113. doi: 10.1097/INF.0000000000001494.

**Long-term Immunogenicity of a Single Dose of Japanese Encephalitis Chimeric Virus Vaccine in Toddlers and Booster Response 5 Years After Primary Immunization.**

[Kosalaraksa P<sup>1</sup>](#), [Watanaveeradej V](#), [Pancharoen C](#), [Capeding MR](#), [Feroldi E](#), [Bouckennooghe A](#).

**BACKGROUND:**

Japanese encephalitis (JE) is an important mosquito-borne viral disease that is endemic in Asia, Western Pacific countries and Northern Australia. Although there is no antiviral treatment, vaccination is effective in preventing this disease.

**METHODS:**

We followed a cohort of 596 children for 5 years after primary vaccination at 12-18 months of age with JE chimeric virus vaccine (JE-CV; IMOJEV) in a multicenter, phase III trial in Thailand and the Philippines to assess antibody persistence and safety. At the end of the 5 years, a subgroup of 85 participants, at 1 site in Thailand, was followed after administration of a JE-CV booster vaccination. JE antibody titers were measured annually after primary vaccination and 28 days after booster vaccination using a 50% plaque reduction neutralization test. Seroprotection was defined as a JE-CV neutralizing antibody titer  $\geq 10$  (1/dil). Kaplan-Meier survival analysis was used to estimate the proportion of participants maintaining protective JE-CV neutralizing antibody titers.

**RESULTS:**

**At 1, 2, 3, 4 and 5 years after vaccination with JE-CV, 88.5%, 82.9%, 78.2%, 74.0% and 68.6% of the participants followed remained seroprotected.** Geometric mean titers in the subgroup assessed after receipt of a booster dose increased from 61.2 (95% confidence interval: 43.8-85.7) pre-booster to 4951 (95% confidence interval: 3928-6241) 28 days post-booster, with all participants seroprotected. There were no safety concerns identified.

**CONCLUSIONS:**

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Protective immune responses persisted for at least 5 years after a JE-CV primary immunization in the majority of participants. JE-CV booster induced a robust immune response even after a 5-year interval.

### Malaria vaccine

[Lancet Infect Dis](#). 2016 Oct;16(10):1134-44. doi: 10.1016/S1473-3099(16)30161-X. Epub 2016 Jul 7.

#### **Safety and immunogenicity of RTS,S/AS01 malaria vaccine in infants and children with WHO stage 1 or 2 HIV disease: a randomised, double-blind, controlled trial.**

[Otieno L](#)<sup>1</sup>, [Onoko M](#)<sup>2</sup>, [Otieno W](#)<sup>3</sup>, [Abuodha J](#)<sup>2</sup>, [Owino E](#)<sup>3</sup>, [Odero C](#)<sup>2</sup>, [Mendoza YG](#)<sup>4</sup>, [Andagalu B](#)<sup>3</sup>, [Awino N](#)<sup>2</sup>, [Ivinson K](#)<sup>5</sup>, [Heerwegh D](#)<sup>4</sup>, [Otsyula N](#)<sup>3</sup>, [Oziemkowska M](#)<sup>2</sup>, [Usuf EA](#)<sup>4</sup>, [Otieno A](#)<sup>3</sup>, [Otieno K](#)<sup>2</sup>, [Leboulleux D](#)<sup>5</sup>, [Leach A](#)<sup>4</sup>, [Oyieko J](#)<sup>3</sup>, [Slutsker L](#)<sup>6</sup>, [Lievens M](#)<sup>4</sup>, [Cowden J](#)<sup>3</sup>, [Lapierre D](#)<sup>4</sup>, [Kariuki S](#)<sup>2</sup>, [Ogutu B](#)<sup>3</sup>, [Vekemans J](#)<sup>4</sup>, [Hamel MJ](#)<sup>6</sup>.

#### **BACKGROUND:**

Malaria remains a major global public health concern, especially in sub-Saharan Africa. The RTS,S/AS01 malaria candidate vaccine was reviewed by the European Medicines Agency and received a positive scientific opinion; WHO subsequently recommended pilot implementation in sub-Saharan African countries. Because malaria and HIV overlap geographically, HIV-infected children should be considered for RTS,S/AS01 vaccination. We therefore aimed to assess the safety of RTS,S/AS01 in HIV-infected children at two sites in western Kenya.

#### **METHODS:**

We did a randomised, double-blind, controlled trial at the clinical trial sites of the Kenya Medical Research Institute (KEMRI)-Walter Reed Army Institute of research in Kisumu and the KEMRI/US Centers for Disease Control and Prevention in Siaya. **Eligible participants were infants and children aged from 6 weeks to 17 months with WHO stage 1 or 2 HIV disease** (documented positive by DNA PCR), whether or not they were receiving antiretroviral therapy (ART). **We randomly assigned participants (1:1) to receive three doses of either RTS,S/AS01 or rabies vaccine (both 0.5 mL per dose by intramuscular injection), given once per month at 0, 1, and 2 months.** We did the treatment allocation using a web-based central randomisation system stratified by age (6 weeks-4 months, 5-17 months), and by baseline CD4% (<10, 10-14, 15-19, and ≥20). Data were obtained in an observer-blind manner, and the vaccine recipient, their parent or carer, the funder, and investigators responsible for the assessment of endpoints were all masked to treatment allocation (only staff responsible for the preparation and administration of the vaccines were aware of the assignment and these individuals played no other role in the study). We provided ART, even if the participants were not receiving ART before the study, and daily co-trimoxazole for prevention of opportunistic infections. **The primary outcome was the occurrence of serious adverse events until 14 months after dose 1 of the vaccine,** assessed in the intention-to-treat population. This trial was registered at ClinicalTrials.gov, number [NCT01148459](#).

#### **FINDINGS:**

Between July 30, 2010, and May 24, 2013, **we enrolled 200 children to our study and randomly assigned 99 to receive RTS,S/AS01 and 101 to receive rabies vaccine.** 177 (89%) of the 200 children enrolled completed 14 months of follow-up. Serious adverse events were noted in 41 (41.4%, 95% CI 31.6-51.8) of 99 RTS,S/AS01 recipients and 37 (36.6%, 27.3-46.8) of 101 rabies-vaccine recipients (relative risk 1.1, 95% CI 0.8-1.6). 20 (20.2%, 95% CI 12.8-29.5) of 99 RTS,S/AS01 recipients and 12 (11.9%, 6.3-19.8) of 101 rabies-vaccine recipients had at least one serious adverse event within 30 days after vaccination, mainly pneumonia, febrile convulsions, and salmonella sepsis. Five (5.1%, 95% CI 1.7-11.4) of 99

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RTS,S/AS01 recipients and four (4.0%, 1.1-9.8) of 101 rabies-vaccine recipients died, but no deaths were deemed related to vaccination. Mortality was associated with five cases of pneumonia (1% RTS,S/AS01 recipients vs 3% rabies-vaccine recipients), five cases of gastroenteritis (3% RTS,S/AS01 recipients vs 2% rabies-vaccine recipients), five cases of malnutrition (2% RTS,S/AS01 recipients vs 3% rabies-vaccine recipients), one case of sepsis (1% rabies-vaccine recipients), one case of *Haemophilus influenzae* meningitis (1% rabies-vaccine recipients), and one case of tuberculosis (1% RTS,S/AS01 recipients).

### INTERPRETATION:

**RTS, S/AS01 was well tolerated when given to children with WHO clinical stage 1 or 2 HIV disease along with high antiretroviral and co-trimoxazole use.** Children with HIV disease could be included in future RTS,S/AS01 vaccination programmes.

[http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(16\)30161-X/fulltext](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30161-X/fulltext)

## Measles vaccine

[Hum Vaccin Immunother.](#) 2017 Mar 31:1-8. doi: 10.1080/21645515.2017.1302629. [Epub ahead of print]

**Immunogenicity and safety of a novel MMR vaccine (live, freeze-dried) containing the Edmonston-Zagreb measles strain, the Hoshino mumps strain, and the RA 27/3 rubella strain: Results of a randomized, comparative, active controlled phase III clinical trial.**

[Sood A](#)<sup>1</sup>, [Mitra M](#)<sup>2</sup>, [Joshi HA](#)<sup>3</sup>, [Nayak US](#)<sup>4</sup>, [Siddaiah P](#)<sup>5</sup>, [Babu TR](#)<sup>6</sup>, [Mahapatro S](#)<sup>7</sup>, [Sanmukhani J](#)<sup>8</sup>, [Gupta G](#)<sup>9</sup>, [Mittal R](#)<sup>10</sup>, [Glueck R](#)<sup>11</sup>.

### Abstract

**This phase III clinical trial was conducted to evaluate the immunogenicity and safety of the single-dose and multi-dose formulations of a novel MMR vaccine** (live, freeze-dried) developed by M/s Cadila Healthcare Limited, India (Cadila MMR vaccine), containing the Hoshino mumps strain, compared to that of an existing MMR vaccine (live, freeze-dried) developed by M/s Serum Institute of India Limited, India (Serum MMR vaccine). These two vaccines have similar measles and rubella strains, but different mumps strains (Hoshino in Cadila MMR vaccine, and L-Zagreb in Serum MMR vaccine). Three hundred and twenty-eight subjects of either sex, aged 15-18 months, were randomized in a 2:1 ratio to receive either the Cadila or Serum MMR vaccine. Immunogenicity assessments (IgG antibodies against measles, mumps, and rubella viruses) were done at baseline and 42 d after vaccination. Solicited (local and systemic) and unsolicited adverse events were recorded for up to 42 d following vaccination. **The Cadila MMR vaccine was found to be non-inferior to the Serum MMR vaccine in terms of end-of-study proportion of subjects seropositive for anti-measles antibodies (100.0% in both groups), anti-mumps antibodies (94.5% vs. 94.0%), and anti-rubella antibodies (95.5% vs. 91.0%).** Both vaccines were well tolerated by all study participants; the most common adverse event reported in both groups was fever, followed by rash. The results of this phase III clinical trial show that the novel Cadila MMR vaccine is non-inferior to the Serum MMR vaccine.

Free access: <http://www.tandfonline.com/doi/full/10.1080/21645515.2017.1302629>

## Meningococcal vaccine



## Pneumococcal vaccine

[Vaccine Rep.](#) 2016 Dec;6:36-43. doi: 10.1016/j.vacrep.2016.08.002.

### **Limited impact of neonatal or early infant schedules of 7-valent pneumococcal conjugate vaccination on nasopharyngeal carriage of *Streptococcus pneumoniae* in Papua New Guinean children: A randomized controlled trial.**

[Aho C](#)<sup>1,2</sup>, [Michael A](#)<sup>1</sup>, [Yoannes M](#)<sup>1</sup>, [Greenhill A](#)<sup>1,3,4</sup>, [Jacoby P](#)<sup>4</sup>, [Reeder J](#)<sup>1,5</sup>, [Pomat W](#)<sup>1,4</sup>, [Saleu G](#)<sup>1</sup>, [Namuigi P](#)<sup>1</sup>, [Phuanukoonnon S](#)<sup>1,6</sup>, [Smith-Vaughan H](#)<sup>2</sup>, [Leach AJ](#)<sup>2</sup>, [Richmond P](#)<sup>7</sup>, [Lehmann D](#)<sup>4</sup>; [Neonatal Pneumococcal Conjugate Vaccine Trial Study Team](#).

#### **Abstract**

*Streptococcus pneumoniae* is a leading cause of pneumonia, the most common cause of childhood death. Papua New Guinean children experience high rates of nasopharyngeal pneumococcal colonization within weeks of birth, predisposing them to pneumococcal disease. In a trial to determine the safety and immunogenicity of early infant vaccination with 7-valent pneumococcal conjugate vaccine (7vPCV), we investigated the impact of early schedules on pneumococcal carriage. **Infants were randomized at birth to receive 7vPCV in a 0-1-2-month (n = 101) or a 1-2-3-month (n = 105) schedule or no 7vPCV (n = 106). All children received 23-valent pneumococcal polysaccharide vaccine at age 9 months.** We cultured nasopharyngeal swabs (NPS) collected at ages 1, 2, 3, 4 weeks and 3, 9, 18 months, and middle ear discharge if present. Pneumococcal serotypes were identified by the Quellung reaction. A total of 1761 NPS were cultured. **The prevalence of pneumococcal carriage was 22% at 1 week of age, rising to 80% by age 3 months and remained >70% thereafter, with high-density carriage in 42% of pneumococcus-positive samples.** We identified 63 different serotypes; 43% of isolates from controls were 13vPCV serotypes. **There were no significant differences in 7vPCV serotype carriage between 7vPCV recipients and controls at any age (22% vs. 31% at 9 months, p = 0.2). At age 9 months the prevalence of non-7vPCV carriage was 17% higher in 7vPCV recipients (48%) than in controls (25%, p = 0.02).** More non-7vPCV serotypes were isolated from ear discharge in 16 7vPCV recipients than from 4 controls (48% vs. 25%, p = 0.13). **The limited impact of neonatal or accelerated infant 7vPCV schedules on vaccine serotype carriage is probably due to the early onset of dense carriage of a broad range of pneumococcal serotypes.** While serotype-independent pneumococcal vaccines are needed in high-risk populations, the underlying environmental factors and sources of infection must be investigated.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5446595/>

[Medicine \(Baltimore\)](#). 2017 Jan;96(2):e5881. doi: 10.1097/MD.0000000000005881.

### **Vaccination with 10-valent pneumococcal conjugate vaccine in infants according to HIV status.**

[Madhi SA](#)<sup>1</sup>, [Koen A](#), [Jose L](#), [van Niekerk N](#), [Adrian PV](#), [Cutland C](#), [François N](#), [Ruiz-Guiñazú J](#), [Yarzabal JP](#), [Moreira M](#), [Borys D](#), [Schuerman L](#).

#### **BACKGROUND:**

Phase III, open-label, single-center, controlled study in South Africa (ClinicalTrials.gov: [NCT00829010](#)) to evaluate immunogenicity, reactogenicity, and safety of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in human immunodeficiency virus (HIV)-infected (HIV+), HIV-exposed-uninfected (HEU), and HIV-unexposed-uninfected (HUU) children.

#### **METHODS:**



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Children stratified by HIV status received PHiD-CV primary vaccination (age 6/10/14 weeks; coadministered with routine childhood vaccines) and booster dose (age 9-10 months). Immune responses, assessed using enzyme-linked immunosorbent and functional assays, and safety were evaluated up to 14 months post-booster.

### RESULTS:

Of 83, 101, and 100 children enrolled in HIV+, HEU, and HUU groups, 70, 91, and 93 were included in according-to-protocol immunogenicity cohort. For each vaccine-serotype, percentages of children with antibody concentrations  $\geq 0.2 \mu\text{g/mL}$  were  $\geq 97\%$  1 month post-primary vaccination and  $\geq 98.5\%$  1 month post-booster (except for 6B and 23F at both timepoints). Post-primary vaccination, functional antibody responses were lower in HIV+ children: for each vaccine-serotype, percentages of children with opsonophagocytic activity (OPA) titres  $\geq 8$  were  $\geq 72\%$ ,  $\geq 81\%$ , and  $\geq 79\%$  for HIV+, HEU, and HUU children. Post-booster,  $\geq 87\%$  of children in each group had OPA titres  $\geq 8$ . Reactogenicity was similar across groups. Thirty one (37%) HIV+, 25 (25%) HEU, and 20 (20%) HUU children reported  $\geq 1$  serious adverse event. Five HIV+ and 4 HEU children died. One death (sudden infant death syndrome; HEU group; 3 days post-dose 1) was considered potentially vaccine-related.

### CONCLUSION:

PHiD-CV was immunogenic and well-tolerated in HIV+, HEU, and HUU children, and has the potential to provide substantial benefit irrespective of HIV infection status.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5266190/>

## Polio vaccine

[Lancet](#). 2016 Jul 9;388(10040):158-69. doi: 10.1016/S0140-6736(16)00703-0. Epub 2016 May 19.

### Humoral and intestinal immunity induced by new schedules of bivalent oral poliovirus vaccine and one or two doses of inactivated poliovirus vaccine in Latin American infants: an open-label randomised controlled trial.

[Asturias EJ](#)<sup>1</sup>, [Bandyopadhyay AS](#)<sup>2</sup>, [Self S](#)<sup>3</sup>, [Rivera L](#)<sup>4</sup>, [Saez-Llorens X](#)<sup>5</sup>, [Lopez E](#)<sup>6</sup>, [Melgar M](#)<sup>7</sup>, [Gaensbauer JT](#)<sup>8</sup>, [Weldon WC](#)<sup>9</sup>, [Oberste MS](#)<sup>9</sup>, [Borate BR](#)<sup>3</sup>, [Gast C](#)<sup>3</sup>, [Clemens R](#)<sup>10</sup>, [Orenstein W](#)<sup>11</sup>, [O'Ryan G M](#)<sup>12</sup>, [Jimeno J](#)<sup>13</sup>, [Clemens SA](#)<sup>10</sup>, [Ward J](#)<sup>14</sup>, [Rüttimann R](#)<sup>15</sup>; [Latin American IPV001BMG Study Group](#).

### BACKGROUND:

Replacement of the trivalent oral poliovirus vaccine (tOPV) with bivalent types 1 and 3 oral poliovirus vaccine (bOPV) and global introduction of inactivated poliovirus vaccine (IPV) are major steps in the polio endgame strategy. In this study, we assessed humoral and intestinal immunity in Latin American infants after three doses of bOPV combined with zero, one, or two doses of IPV.

### METHODS:

This open-label randomised controlled multicentre trial was part of a larger study. 6-week-old full-term infants due for their first polio vaccinations, who were healthy on physical examination, with no obvious medical conditions and no known chronic medical disorders, were enrolled from four investigational sites in Colombia, Dominican Republic, Guatemala, and Panama. The infants were randomly assigned by permuted block randomisation (through the use of a computer-generated list, block size 36) to nine groups, of which five will be discussed in this report. These five groups were randomly assigned 1:1:1:1 to four permutations of schedule: groups 1 and 2 (control groups) received bOPV at 6, 10, and 14 weeks; group 3 (also a control group, which did not count as a permutation) received tOPV at 6, 10, and 14 weeks; group 4

received bOPV plus one dose of IPV at 14 weeks; and group 5 received bOPV plus two doses of IPV at 14 and 36 weeks. Infants in all groups were challenged with monovalent type 2 vaccine (mOPV2) at 18 weeks (groups 1, 3, and 4) or 40 weeks (groups 2 and 5). **The primary objective was to assess the superiority of bOPV-IPV schedules over bOPV alone, as assessed by the primary endpoints of humoral immunity (neutralising antibodies-ie, seroconversion) to all three serotypes and intestinal immunity (faecal viral shedding post-challenge) to serotype 2, analysed in the per-protocol population.** Serious and medically important adverse events were monitored for up to 6 months after the study vaccination. This study is registered with ClinicalTrials.gov, number [NCT01831050](https://clinicaltrials.gov/ct2/show/study/NCT01831050), and has been completed.

### FINDINGS:

Between May 20, 2013, and Aug 15, 2013, 940 eligible infants were enrolled and randomly assigned to the five treatment groups (210 to group 1, 210 to group 2, 100 to group 3, 210 to group 4, and 210 to group 5). One infant in group 1 was not vaccinated because their parents withdrew consent after enrolment and randomisation, so 939 infants actually received the vaccinations. Three doses of bOPV or tOPV elicited type 1 and 3 seroconversion rates of at least 97.7%. **Type 2 seroconversion occurred in 19 of 198 infants (9.6%, 95% CI 6.2-14.5) in the bOPV-only groups, 86 of 88 (97.7%, 92.1-99.4) in the tOPV-only group (p<0.0001 vs bOPV-only), and 156 of 194 (80.4%, 74.3-85.4) infants in the bOPV-one dose of IPV group (p<0.0001 vs bOPV-only).** A further 20 of 193 (10%) infants in the latter group seroconverted 1 week after mOPV2 challenge, resulting in around 98% of infants being seropositive against type 2. **After a bOPV-two IPV schedule, all 193 infants (100%, 98.0-100; p<0.0001 vs bOPV-only) seroconverted to type 2.** IPV induced small but significant decreases in a composite serotype 2 viral shedding index after mOPV2 challenge. 21 serious adverse events were reported in 20 patients during the study, including two that were judged to be possibly related to the vaccines. Most of the serious adverse events (18 [86%] of 21) and 24 (80%) of the 30 important medical events reported were infections and infestations. No deaths occurred during the study.

### INTERPRETATION:

**bOPV provided humoral protection similar to tOPV against polio serotypes 1 and 3. After one or two IPV doses in addition to bOPV, 80% and 100% of infants seroconverted, respectively, and the vaccination induced a degree of intestinal immunity against type 2 poliovirus.**

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)00703-0/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00703-0/fulltext)

[J Infect Dis.](#) 2017 Feb 15;215(4):529-536. doi: 10.1093/infdis/jiw595.

### **The Duration of Intestinal Immunity After an Inactivated Poliovirus Vaccine Booster Dose in Children Immunized With Oral Vaccine: A Randomized Controlled Trial.**

[John J<sup>1</sup>](#), [Giri S<sup>2</sup>](#), [Karthikeyan AS<sup>2</sup>](#), [Lata D<sup>2</sup>](#), [Jeyapaul S<sup>1</sup>](#), [Rajan AK<sup>3</sup>](#), [Kumar N<sup>2</sup>](#), [Dhanapal P<sup>2</sup>](#), [Venkatesan J<sup>2</sup>](#), [Mani M<sup>2</sup>](#), [Hanusha J<sup>2</sup>](#), [Raman U<sup>2</sup>](#), [Moses PD<sup>3</sup>](#), [Abraham A<sup>3</sup>](#), [Bahl S<sup>4</sup>](#), [Bandyopadhyay AS<sup>5</sup>](#), [Ahmad M<sup>6</sup>](#), [Grassly NC<sup>7</sup>](#), [Kang G<sup>2</sup>](#).

### **Background.:**

In 2014, 2 studies showed that inactivated poliovirus vaccine (IPV) boosts intestinal immunity in children previously immunized with oral poliovirus vaccine (OPV). As a result, IPV was introduced in mass campaigns to help achieve polio eradication.

### **Methods.:**

We conducted an open-label, randomized, controlled trial to assess the duration of the boost in intestinal immunity following a dose of IPV given to OPV-immunized children. Nine hundred healthy children in Vellore, India, aged 1-4 years were randomized (1:1:1) to receive IPV at 5

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months (arm A), at enrollment (arm B), or no vaccine (arm C). The primary outcome was poliovirus shedding in stool 7 days after bivalent OPV challenge at 11 months.

### Results.:

For children in arms A, B, and C, 284 (94.7%), 297 (99.0%), and 296 (98.7%), respectively, were eligible for primary per-protocol analysis. Poliovirus shedding 7 days after challenge was less prevalent in arms A and B compared with C (24.6%, 25.6%, and 36.4%, respectively; risk ratio 0.68 [95% confidence interval: 0.53-0.87] for A versus C, and 0.70 [0.55-0.90] for B versus C).

### Conclusions.:

**Protection against poliovirus remained elevated 6 and 11 months after an IPV boost, although at a lower level than reported at 1 month.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5388294/>

## Rotavirus vaccine

[N Engl J Med](#). 2017 Mar 23;376(12):1121-1130. doi: 10.1056/NEJMoa1609462.

### Efficacy of a Low-Cost, Heat-Stable Oral Rotavirus Vaccine in Niger.

[Isanaka S<sup>1</sup>](#), [Guindo O<sup>1</sup>](#), [Langendorf C<sup>1</sup>](#), [Matar Seck A<sup>1</sup>](#), [Plikaytis BD<sup>1</sup>](#), [Sayinzoga-Makombe N<sup>1</sup>](#), [McNeal MM<sup>1</sup>](#), [Meyer N<sup>1</sup>](#), [Adehossi E<sup>1</sup>](#), [Djibo A<sup>1</sup>](#), [Jochum B<sup>1</sup>](#), [Grais RF<sup>1</sup>](#).

### BACKGROUND:

Each year, rotavirus gastroenteritis is responsible for about 37% of deaths from diarrhea among children younger than 5 years of age worldwide, with a disproportionate effect in sub-Saharan Africa.

### METHODS:

We conducted a randomized, placebo-controlled trial in Niger to evaluate the efficacy of a live, oral bovine rotavirus pentavalent vaccine (BRV-PV, Serum Institute of India) to prevent severe rotavirus gastroenteritis. **Healthy infants received three doses of the vaccine or placebo at 6, 10, and 14 weeks of age.** Episodes of gastroenteritis were assessed through active and passive surveillance and were graded on the basis of the score on the Vesikari scale (which ranges from 0 to 20, with higher scores indicating more severe disease). **The primary end point was the efficacy of three doses of vaccine as compared with placebo against a first episode of laboratory-confirmed severe rotavirus gastroenteritis (Vesikari score,  $\geq 11$ ) beginning 28 days after dose 3.**

### RESULTS:

Among the 3508 infants who were included in the per-protocol efficacy analysis, **there were 31 cases of severe rotavirus gastroenteritis in the vaccine group and 87 cases in the placebo group (2.14 and 6.44 cases per 100 person-years, respectively), for a vaccine efficacy of 66.7% (95% confidence interval [CI], 49.9 to 77.9).** Similar efficacy was seen in the intention-to-treat analyses, which showed a vaccine efficacy of 69.1% (95% CI, 55.0 to 78.7). There was no significant between-group difference in the risk of adverse events, which were reported in 68.7% of the infants in the vaccine group and in 67.2% of those in the placebo group, or in the risk of serious adverse events (in 8.3% in the vaccine group and in 9.1% in the placebo group); there were 27 deaths in the vaccine group and 22 in the placebo group. **None of the infants had confirmed intussusception.**

### CONCLUSIONS:

Three doses of BRV-PV, an oral rotavirus vaccine, had an efficacy of 66.7% against severe rotavirus gastroenteritis among infants in Niger.

Free access: <http://www.nejm.org/doi/full/10.1056/NEJMoal609462#t=articleMethods>

[Heliyon](#). 2017 May 16;3(5):e00302. doi: 10.1016/j.heliyon.2017.e00302. eCollection 2017 May. **ROTAVAC® does not interfere with the immune response to childhood vaccines in Indian infants: A randomized placebo controlled trial.**

[Chandola TR](#)<sup>1,2</sup>, [Taneja S](#)<sup>1,2</sup>, [Goyal N](#)<sup>1,2</sup>, [Antony K](#)<sup>3</sup>, [Bhatia K](#)<sup>1,2</sup>, [More D](#)<sup>3,1</sup>, [Bhandari N](#)<sup>1,2</sup>, [Choi I](#)<sup>4</sup>, [Mohan K](#)<sup>5</sup>, [Prasad S](#)<sup>5</sup>, [Harshavardhan G](#)<sup>5</sup>, [Rao TS](#)<sup>6,7</sup>, [Vrati S](#)<sup>8</sup>, [Bhan MK](#)<sup>9</sup>.

#### Abstract

A phase III randomized double-blind placebo-controlled trial was conducted in the urban neighborhoods of Delhi to assess whether Oral Rotavirus Vaccine ROTAVAC® interferes with the immune response to childhood vaccines when coadministered. **Infants aged 6 weeks were randomized to receive three doses of either ROTAVAC® or placebo along with childhood vaccines:** Oral Polio Vaccine and vaccines against Diphtheria, Pertussis, Tetanus, Hepatitis B and *Haemophilus influenza* type b given as Pentavalent at 6, 10, 14 weeks of age. Blood specimens were collected from all infants at baseline and 4 weeks post dose 3 to assess the immune response to antigens in Oral Polio Vaccine, Pentavalent and ROTAVAC® vaccines. **Non-inferiority of immune response to all vaccine components of the childhood vaccines when ROTAVAC® was administered concurrently was demonstrated.** Non-inferior immune responses to childhood vaccines were evaluated based on the seroprotective levels of antibodies against polio types 1, 2, and 3, Diphtheria toxoid, Tetanus toxoid, *Haemophilus influenza* type b anti- polyribosyl ribitol phosphate antibodies and Hepatitis B antibodies; and the Geometric Mean Concentration for Pertussis. The proportion of infants who seroconverted ( $\geq 4$  fold rise) was 38.6% in the ROTAVAC® group and 12.2% in the placebo group. The frequency and severity of immediate adverse events, adverse events and serious adverse events were similar in both groups. None of the five reported deaths were considered to be related to the ROTAVAC® and no case of intussusception meeting Brighton Diagnostic Certainty Level I criteria was reported. This study demonstrated that ROTAVAC® can be safely administered with childhood vaccines without interfering with the immune response to the antigens contained in these vaccines.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5435614/>

[PLoS Med](#). 2017 Apr 18;14(4):e1002282. doi: 10.1371/journal.pmed.1002282. eCollection 2017 Apr.

**Effectiveness of a live oral human rotavirus vaccine after programmatic introduction in Bangladesh: A cluster-randomized trial.**

[Zaman K](#)<sup>1</sup>, [Sack DA](#)<sup>2</sup>, [Neuzil KM](#)<sup>3</sup>, [Yunus M](#)<sup>1</sup>, [Moulton LH](#)<sup>2</sup>, [Sugimoto JD](#)<sup>4</sup>, [Fleming JA](#)<sup>3</sup>, [Hossain I](#)<sup>1</sup>, [Arifeen SE](#)<sup>1</sup>, [Azim T](#)<sup>1</sup>, [Rahman M](#)<sup>1</sup>, [Lewis KDC](#)<sup>3</sup>, [Feller AJ](#)<sup>2</sup>, [Qadri F](#)<sup>1</sup>, [Halloran ME](#)<sup>4,5</sup>, [Cravioto A](#)<sup>1</sup>, [Victor JC](#)<sup>3</sup>.

#### BACKGROUND:

Rotavirus vaccines are now globally recommended by the World Health Organization (WHO), but in early 2009 WHO's Strategic Advisory Group of Experts on Immunization reviewed available data and concluded that there was no evidence for the efficacy or effectiveness of a two-dose schedule of the **human rotavirus vaccine** (HRV; Rotarix) given early at 6 and 10 wk of age. Additionally, the effectiveness of programmatic rotavirus vaccination, including possible indirect effects, has not been assessed in low-resource populations in Asia.

#### METHODS AND FINDINGS:

In Bangladesh, we cluster-randomized (1:1) 142 villages of the Matlab Health and Demographic Surveillance System to **include two doses of HRV with the standard infant vaccines at 6 and 10 wk of age or to provide standard infant vaccines without HRV**. The study was initiated November 1, 2008, and **surveillance was conducted concurrently at Matlab Diarrhoea Hospital and two community treatment centers to identify children less than 2 y of age presenting with acute rotavirus diarrhea (ARD)** through March 31, 2011. Laboratory confirmation was made by enzyme immunoassay detection of rotavirus antigen in stool specimens. **Overall effectiveness of the HRV vaccination program (primary objective) was measured by comparing the incidence rate of ARD among all children age-eligible for vaccination in villages where HRV was introduced to that among such children in villages where HRV was not introduced**. Total effectiveness among vaccinees and indirect effectiveness were also evaluated. In all, 6,527 infants were age-eligible for vaccination in 71 HRV villages, and 5,791 in 71 non-HRV villages. **In HRV villages, 4,808 (73.7%) infants received at least one dose of HRV. The incidence rate of ARD was 4.10 cases per 100 person-years in non-HRV villages compared to 2.8 per 100 person-years in HRV villages, indicating an overall effectiveness of 29.0% (95% CI, 11.3% to 43.1%). The total effectiveness of HRV against ARD among vaccinees was 41.4% (95% CI, 23.2% to 55.2%). The point estimate for total effectiveness was higher against ARD during the first year of life than during the second (45.2% versus 28.9%), but estimates for the second year of life lacked precision and did not reach statistical significance**. Indirect effects were not detected. To check for bias in presentation to treatment facilities, we evaluated the effectiveness of HRV against acute diarrhea associated with enterotoxigenic *Escherichia coli*; it was 4.0% (95% CI, -46.5% to 37.1%), indicating that bias likely was not introduced. Thirteen serious adverse events were identified among recipients of HRV, but none were considered related to receipt of study vaccine. The main limitation of this study is that it was an open-label study with an observed-only control group (no placebo).

### CONCLUSIONS:

**The two-dose HRV rotavirus vaccination program significantly reduced medically attended ARD in this low-resource population in Asia. Protection among vaccinees was similar to that in other low-resource settings**. In low-resource populations with high rotavirus incidence, large-scale vaccination across a wide population may be required to obtain the full benefit of rotavirus vaccination, including indirect effects.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5395158/>

[Malawi Med J](#). 2016 Sep;28(3):108-114.

### Effect of human rotavirus vaccine on severe diarrhea in African infants.

[Madhi SA](#)<sup>1</sup>, [Cunliffe NA](#)<sup>2</sup>, [Steele D](#)<sup>3</sup>, [Witte D](#)<sup>4</sup>, [Kirsten M](#)<sup>5</sup>, [Louw C](#)<sup>6</sup>, [Ngwira B](#)<sup>7</sup>, [Victor JC](#)<sup>8</sup>, [Gillard PH](#)<sup>9</sup>, [Cheuvart BB](#)<sup>9</sup>, [Han HH](#)<sup>9</sup>, [Neuzil KM](#)<sup>8</sup>.

### BACKGROUND:

Rotavirus is the most common cause of severe gastroenteritis among young children worldwide. Data are needed to assess the efficacy of the rotavirus vaccine in African children.

### METHODS:

We conducted a randomized, placebo-controlled, multicenter trial in South Africa (3166 infants; 64.1% of the total) and Malawi (1773 infants; 35.9% of the total) to evaluate the efficacy of a live, oral rotavirus vaccine in preventing severe rotavirus gastroenteritis. Healthy infants were randomly assigned in a 1:1:1 ratio to receive two doses of vaccine (in addition to one dose of placebo) or three doses of vaccine - the pooled vaccine group - or three doses of placebo at 6, 10, and 14 weeks of age. Episodes of gastroenteritis caused by wild-type rotavirus during the



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first year of life were assessed through active follow-up surveillance and were graded with the use of the Vesikari scale.

### RESULTS:

A total of 4939 infants were enrolled and randomly assigned to one of the three groups; 1647 infants received two doses of the vaccine, 1651 infants received three doses of the vaccine, and 1641 received placebo. Of the 4417 infants included in the per-protocol efficacy analysis, severe rotavirus gastroenteritis occurred in 4.9% of the infants in the placebo group and in 1.9% of those in the pooled vaccine group (vaccine efficacy, 61.2%; 95% confidence interval, 44.0 to 73.2). **Vaccine efficacy was lower in Malawi than in South Africa (49.4% vs. 76.9%); however, the number of episodes of severe rotavirus gastroenteritis that were prevented was greater in Malawi than in South Africa (6.7 vs. 4.2 cases prevented per 100 infants vaccinated per year). Efficacy against all-cause severe gastroenteritis was 30.2%.** At least one serious adverse event was reported in 9.7% of the infants in the pooled vaccine group and in 11.5% of the infants in the placebo group.

### CONCLUSIONS:

Human rotavirus vaccine significantly reduced the incidence of severe rotavirus gastroenteritis among African infants during the first year of life. (ClinicalTrials.gov number, [NCT00241644](https://clinicaltrials.gov/ct2/show/study/NCT00241644)).

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5117000/>

[AIDS](#). 2017 Jan 2;31(1):49-59.

### [Safety and immunogenicity of a live attenuated pentavalent rotavirus vaccine in HIV-exposed infants with or without HIV infection in Africa.](#)

[Levin MJ<sup>1</sup>](#), [Lindsey JC](#), [Kaplan SS](#), [Schimana W](#), [Lawrence J](#), [McNeal MM](#), [Bwakura-Dangarembizi M](#), [Ogwu A](#), [Mpabalwani EM](#), [Sato P](#), [Siberry G](#), [Nelson M](#), [Hille D](#), [Weinberg GA](#), [Weinberg A](#).

### OBJECTIVE:

Although many HIV-infected (HIV+) and HIV-exposed but uninfected (HEU) infants have received live rotavirus vaccines since the WHO recommended universal administration of these vaccines to infants, there has been limited prospective information on their safety and immunogenicity in either group of infants.

### DESIGN/METHODS:

**We performed a randomized, double-blinded, placebo-controlled trial of the safety and immunogenicity of oral pentavalent rotavirus vaccine (RV5) administered to HIV+ and HEU infants in four African countries.** Ninety-three percent of HIV+ infants were receiving antiretroviral therapy prior to vaccination. Participants were followed for safety. Immune responses were measured 14 days after three doses of RV5, including serum antirotavirus neutralizing and IgA antibodies, IgA antibody in stool, and antirotavirus memory B and T-cell FluoroSpot. Shedding of RV5 in stool was monitored.

### RESULTS:

A total of 76 HIV+ and 126 HEU infants were enrolled from 2009 to 2013. No significant differences were found in adverse event rates, including grade 3 events, between RV5 and placebo recipients, for either HIV+ or HEU infants. The proportion of antirotavirus IgA responders (at least three-fold increase from baseline) after RV5 administration was 81% in both HIV+ and HEU infants, which was approximately 2.5-fold higher than in placebo recipients ( $P < 0.001$ ). Neutralizing antibody responses to three of five serotypes were significantly higher after RV5 regardless of HIV status, and those of HIV+ infants were equal or greater than responses of HEU infants to all five serotypes. Only one HIV+ RV5 recipient had RV5 isolated from stool.

**CONCLUSION:**

RV5 was immunogenic in both HIV+ and HEU infants and no safety signals were observed.

[Pediatr Infect Dis J.](#) 2017 Jan;36(1):72-78.

**Heterogeneity of Rotavirus Vaccine Efficacy Among Infants in Developing Countries.**

[Gruber JF<sup>1</sup>](#), [Hille DA](#), [Liu GF](#), [Kaplan SS](#), [Nelson M](#), [Goveia MG](#), [Mast TC](#).

**Author information**

**BACKGROUND:**

Rotavirus is the leading cause of severe diarrhea worldwide in young children. Although rotavirus vaccine efficacy is high in developed countries, efficacy is lower in developing countries. Here, we investigated heterogeneity of rotavirus vaccine efficacy by infant characteristics in developing countries.

**METHODS:**

An exploratory, post hoc analysis was conducted using randomized controlled trial data of the pentavalent rotavirus vaccine (RV5) conducted in Africa and Asia ([NCT00362648](#)). Infants received either 3 doses of vaccine/placebo and were followed for up to 2 years. Within subgroups, vaccine efficacies and 95% confidence intervals (CIs) against rotavirus gastroenteritis (RVGE) were estimated using Poisson regression. We assessed heterogeneity of efficacy by age at first dose, gender, breastfeeding status and nutrition status.

**RESULTS:**

African children receiving the first dose at <8 weeks had lower efficacy (23.7%; 95% CI: -8.2%-46.3%) than those vaccinated at ≥8 weeks (59.1%; 95% CI: 34.0%-74.6%). Marginally statistically significant differences were observed by age at first dose, gender and underweight status in Ghana and gender in Asian countries.

**CONCLUSIONS:**

Heterogeneity of efficacy was observed for age at first dose in African countries. This was an exploratory analysis; additional studies are needed to validate these results.

[J Infect Dis.](#) 2017 Mar 1;215(5):786-789. doi: 10.1093/infdis/jix028.

**Secretor and Salivary ABO Blood Group Antigen Status Predict Rotavirus Vaccine Take in Infants.**

[Kazi AM<sup>1</sup>](#), [Cortese MM<sup>2</sup>](#), [Yu Y<sup>3</sup>](#), [Lopman B<sup>2</sup>](#), [Morrow AL<sup>3</sup>](#), [Fleming JA<sup>4</sup>](#), [McNeal MM<sup>5</sup>](#), [Steele AD<sup>4</sup>](#), [Parashar UD<sup>2</sup>](#), [Zaidi AKM<sup>1</sup>](#), [Ali A<sup>1</sup>](#).

**Abstract**

Histo-blood group antigens (HBGAs) expressed on enterocytes are proposed receptors for rotaviruses and can be measured in saliva. Among 181 Pakistani infants in a G1P[8] rotavirus vaccine trial who were seronegative at baseline, **anti-rotavirus immunoglobulin A seroconversion rates after 3 vaccine doses differed significantly by salivary HBGA phenotype**, with the lowest rate (19%) among infants who were nonsecretors (ie, who did not express the carbohydrate synthesized by FUT2), an intermediate rate (30%) among secretors with non-blood group O, and the highest rate (51%) among secretors with O blood group. **Differences in HBGA expression may be responsible for some of the discrepancy in the level of protection detected for the current rotavirus vaccines in low-income versus high-income settings.**

## Salmonella typhi vaccine

## Typhoid vaccine

## Varicella vaccine

[Hum Vaccin Immunother.](#) 2017 May 16;1-6. doi: 10.1080/21645515.2017.1318236. [Epub ahead of print]

### **Safety and immunogenicity of Bio Pox™, a live varicella vaccine (Oka strain) in Indian children: A comparative multicentric, randomized phase II/III clinical trial.**

[Dubey AP](#)<sup>1</sup>, [Faridi MMA](#)<sup>2</sup>, [Mitra M](#)<sup>3</sup>, [Kaur IR](#)<sup>4</sup>, [Dabas A](#)<sup>1</sup>, [Choudhury J](#)<sup>3</sup>, [Mukherjee M](#)<sup>3</sup>, [Mishra D](#)<sup>1</sup>.

#### **Abstract**

Varicella or chickenpox is a highly contagious disease with a high secondary attack rate. Almost 30% of Indian adolescents lack protective antibodies against varicella, emphasizing the need of routine varicella immunization. The Oka VZV is a well-established, safe and efficacious vaccine strain that is highly immunogenic and produces lifelong protective immunity. The present multicentric, open label, randomized, controlled Phase II/III study, compared the Bio Pox™ (indigenous investigational vaccine) with a licensed vaccine, Varivax™, for its safety and immunogenicity profile in 252 healthy subjects in the age group of 1-12 y (cohort I: 6-12 years, II: 1-6 years) in 3 tertiary medical institutions. Antibodies were measured by VZV Glycoprotein Enzyme Linked Immunoassay (IgG ELISA) kit. Seroconversion percentage in children having pre-vaccination anti VZV IgG titer <10 mIU/mL (< 5 gp ELISA units/mL) were 80% for Bio Pox™ and 77% for Varivax™ (p = 0.692). The seroconversion rate in the group receiving Bio Pox™ was non-inferior to the group that received Varivax™. There were mild local reactions for both the vaccines; none of the patient had fever or required hospitalization or medication. The Bio Pox™ was found to be safe and immunogenic in children against VZV infection.

## Vitamin A

[Int J Epidemiol.](#) 2016 Dec 1;45(6):2112-2121. doi: 10.1093/ije/dyw238.

### **The effect of neonatal vitamin A supplementation on morbidity and mortality at 12 months: a randomized trial.**

[Smith ER](#)<sup>1</sup>, [Muhihi A](#)<sup>2</sup>, [Mshamu S](#)<sup>2</sup>, [Sudfeld CR](#)<sup>1</sup>, [Noor RA](#)<sup>2,3</sup>, [Spiegelman D](#)<sup>1,2,4,5</sup>, [Shapiro RL](#)<sup>6</sup>, [Masanja H](#)<sup>7</sup>, [Fawzi W](#)<sup>1,3,5</sup>.

#### **Background:**

Neonatal vitamin A supplementation (NVAS) is an intervention hypothesized to reduce infant morbidity and mortality. The objective of this study was to assess the efficacy of neonatal vitamin A supplementation in reducing infant morbidity and mortality and assess potential sources of heterogeneity of the effect of NVAS.

#### **Methods:**

We completed an individually randomized, double-blind, placebo-controlled trial in Tanzania.

**Infants were randomized within 3 days of birth to a single dose of vitamin A (50 000 IU) or placebo.** We assessed infants at 1 and 3 days after supplementation, as well as 1, 3, 6 and 12 months after supplementation. We included all live births in the analysis and used relative risks

(RR) and 95% confidence intervals (CI) to assess the risks of mortality and hospitalization by 12 months. We used general estimating equations to assess the incidence of morbidities during infancy.

### Results:

**A total of 31 999 infants were enrolled in the study between August 2010 and March 2013. At 12 months, vitamin A did not reduce all-cause infant mortality (RR 1.04; 95% CI 0.92-1.16), nor affect hospitalization (RR 1.09; 95% CI 0.97-1.22) or all-cause morbidity (RR 1.00; 95% CI 0.96-1.05). Postpartum maternal vitamin A supplementation modified the effect of neonatal vitamin A supplementation on mortality at 12 months (P-value, test for interaction = 0.04). Among infants born to women who received a mega-dose of vitamin A after delivery, NVAS appeared to increase the risk of death (RR 1.12; 95% CI 0.98-1.29), whereas the risk of death among infants born to women who did not receive a mega-dose was reduced (RR 0.86; 95% CI 0.70-1.06). We noted no modification of the effect of NVAS by infant gender, birthweight or maternal HIV status.**

### Conclusion:

NVAS did not affect the risk of death or incidence of common childhood morbidities. However, this study sheds light on potential sources of heterogeneity of the effect of neonatal vitamin A supplementation which should be further examined in a pooled analysis of all NVAS trials.

Free access: <https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/dyw238>

[Arch Dis Child](#). 2017 Mar;102(3):216-223. doi: 10.1136/archdischild-2016-310542. Epub 2016 Jun 28.

### Evaluation of the uptake and impact of neonatal vitamin A supplementation delivered through the Lady Health Worker programme on neonatal and infant morbidity and mortality in rural Pakistan: an effectiveness trial.

[Soofi S<sup>1</sup>](#), [Ariff S<sup>1</sup>](#), [Sadiq K<sup>1</sup>](#), [Habib A<sup>1</sup>](#), [Bhatti Z<sup>1</sup>](#), [Ahmad I<sup>1</sup>](#), [Hussain M<sup>1</sup>](#), [Ali N<sup>2</sup>](#), [Cousens S<sup>3</sup>](#), [Bhutta ZA<sup>1,3,4</sup>](#).

### BACKGROUND:

Despite evidence for the benefits of vitamin A supplementation (VAS) among children 6 to 59 months of age, the feasibility of introduction and potential benefit of VAS in the neonatal period in public health programmes is uncertain.

### OBJECTIVE:

The primary objective was to evaluate the feasibility and effectiveness of **early neonatal VAS (single dose of 50 000 international units within 48-72 hours after birth)** delivered through the public sector Lady Health Worker (LHW) programme in rural Pakistan and to document its association with a reduction in mortality at 6 months of age.

### METHODS:

A community-based, cluster randomised, placebo-controlled trial was undertaken in two districts of rural Pakistan. LHWs dispensed vitamin A/placebo in identical capsules to newborn infants within 48-72 hours of birth. Follow-up visits were undertaken at 1 week of age and every 4 weeks thereafter until 6 months of age.

### RESULTS:

Of a total of 15 433 consecutive pregnancies among eligible women of reproductive age, 13 225 pregnancies were registered, 12 218 live births identified and 11 028 newborn infants reached by LHWs. Of these, 5380 (49%) received neonatal VAS and 5648 (51%) placebo. The LHWs successfully delivered the capsules to 79% of newborns within 72 hours of birth with no significant adverse effects. Although the proportion of days observed with symptoms of fever,

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diarrhoea or rapid breathing were lower with neonatal VAS, these differences were not statistically significant. Mortality rates in the two groups were comparable at 6 months of age.

### CONCLUSIONS:

While our study demonstrated that neonatal VAS was safe and could be feasibly delivered by LHWs in Pakistan as part of their early postnatal visits, the overall lack of benefit on neonatal and 6-month morbidity and mortality in our population suggests the need for further evaluation of this intervention in populations at risk.

Free access: <http://adc.bmj.com/content/102/3/216.long>

[J Nutr.](#) 2016 Dec;146(12):2551-2558. Epub 2016 Oct 19.

### [Provitamin A Carotenoid-Biofortified Maize Consumption Increases Pupillary Responsiveness among Zambian Children in a Randomized Controlled Trial.](#)

[Palmer AC](#)<sup>1</sup>, [Healy K](#)<sup>2</sup>, [Barffour MA](#)<sup>2</sup>, [Siamusantu W](#)<sup>3</sup>, [Chileshe J](#)<sup>4</sup>, [Schulze KJ](#)<sup>2</sup>, [West KP Jr](#)<sup>2</sup>, [Labrique AB](#)<sup>2</sup>.

### BACKGROUND:

Impaired dark adaptation is an early functional indicator of vitamin A deficiency that may be prevented by regular dietary intake of foods containing provitamin A carotenoids.

### OBJECTIVE:

We tested the impact of provitamin A carotenoid-biofortified maize consumption (~ 15 µg β-carotene/g) on dark adaptation in Zambian children.

### METHODS:

We used a cluster-randomized trial of children aged 4-8 y (n = 1024) in Mkushi District, Zambia, and compared the regular consumption (2 meals/d, 6 d/wk for 6 mo) of biofortified orange maize (OM) to white maize (WM). The primary outcome was the serum retinol response. In a random sample (n = 542), we used a digital pupillometer to test pre- and postintervention responses to graded light stimuli (-2.9 to 0.1 log cd/m<sup>2</sup>) in a dark-adapted state.

### RESULTS:

At baseline, 11.7% of the children had serum retinol <0.7 µmol/L, 14.4% had impaired dark adaptation (pupillary threshold ≥ -1.11 log cd/m<sup>2</sup>), and 2.3% had night blindness. The mean ± SD pupillary responsiveness to light stimuli was poorer at baseline in the OM group (16.1% ± 6.6%) than the WM group (18.1% ± 6.4%) (P = 0.02) but did not differ at follow-up (OM: 17.6% ± 6.5%; WM: 18.3% ± 6.5%). Among children with serum retinol <1.05 µmol/L at baseline, there was greater improvement in pupillary responsiveness in the OM group (2.2%; 95% CI: 0.1%, 4.3%) than the WM group (0.2%; 95% CI: -1.1%, 1.5%; P = 0.01), but there were no differences in children with adequate baseline status. We found no effect of treatment on pupillary threshold or night blindness.

### CONCLUSIONS:

The regular consumption of provitamin A carotenoid-biofortified maize increased pupillary responsiveness among children with marginal or deficient vitamin A status, providing evidence of a functional benefit to consuming this biofortified crop. This trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as [NCT01695148](#).

## Vitamin D

(See also Neonates – preterm and low birth weight)



[PLoS One](#). 2017 Mar 8;12(3):e0170509. doi: 10.1371/journal.pone.0170509. eCollection 2017.  
**Vitamin-D deficiency predicts infections in young north Indian children: A secondary data analysis.**

[Chowdhury R](#)<sup>1</sup>, [Taneja S](#)<sup>1</sup>, [Bhandari N](#)<sup>1</sup>, [Sinha B](#)<sup>1</sup>, [Upadhyay RP](#)<sup>1</sup>, [Bhan MK](#)<sup>2,3</sup>, [Strand TA](#)<sup>4,5</sup>.

**BACKGROUND:**

Recent studies have demonstrated a relationship between poor vitamin D status and respiratory infections and diarrhea among young children. Acute lower respiratory infections (ALRI) and diarrhea are among the two most important causes of death in under-5 children. In this paper, **we examined the extent to which vitamin-D deficiency (<10 ng/ml) predicts ALRI, clinical pneumonia and diarrhea among 6 to 30 months old children.**

**METHODS:**

We used data from a randomized controlled trial (RCT) of daily folic acid and/or vitamin B12 supplementation for six months in 6 to 30 months old children conducted in Delhi, India. Generalized estimating equations (GEE) were used to examine the associations between vitamin-D deficiency and episodes of ALRI, clinical pneumonia and diarrhea.

**RESULTS:**

**Of the 960 subjects who had vitamin-D concentrations measured, 331(34.5%) were vitamin-D deficient.** We found, after controlling for relevant potential confounders (age, sex, breastfeeding status, wasting, stunting, underweight, anemia status and season), that **the risk of ALRI was significantly higher among vitamin-D deficient (OR 1.26; 95% CI: 1.03 to 1.55) compared to vitamin-D-replete children in the six months follow-up period.** Vitamin-D status was not associated with episodes of diarrhea or clinical pneumonia.

**CONCLUSION:**

**Vitamin-D deficiency is common in young children in New Delhi and is associated with a higher risk of ALRI.** The role of vitamin D in Indian children needs to be elucidated in further studies.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5342185/>

[Indian Pediatr](#). 2016 Nov 15;53(11):967-976.

**Vitamin D Supplementation for Treatment and Prevention of Pneumonia in Under-five Children: A Randomized Double-blind Placebo Controlled Trial.**

[Gupta P](#)<sup>1</sup>, [Dewan P](#), [Shah D](#), [Sharma N](#), [Bedi N](#), [Kaur IR](#), [Bansal AK](#), [Madhu SV](#).

**OBJECTIVE:**

To evaluate the efficacy of single oral mega-dose of Vitamin D3 for treatment and prevention of pneumonia in under-five children.

**DESIGN:**

Randomized, double blind, placebo-controlled trial.

**SETTING:**

Tertiary-care hospital.

**PARTICIPANTS:**

**324 children (of 980 assessed) between 6 mo-5 y age (median (IQR): 12 (7,19.8) mo) with WHO-defined severe pneumonia.** Of these, 126 (39%) were vitamin D deficient (serum 25(OH)D <12 ng/mL).

**INTERVENTION:**

100,000 IU of oral cholecalciferol (n= 162) or placebo (n= 162) in single dose, administered at enrolment. Outcome variables: Primary: **Time to resolution of severe pneumonia and proportion of children having recurrence of pneumonia in next 6 months;** Secondary:

Change in serum levels of 25(OH)D; immunoglobulins IgA, IgG, IgM, and cathelicidin 2 weeks following supplementation; and time taken for overall resolution of illness.

### OUTCOME VARIABLES:

Primary: Time to resolution of severe pneumonia and proportion of children having recurrence of pneumonia in next 6 months; Secondary: Change in serum levels of 25(OH)D; immunoglobulins IgA, IgG, IgM, and cathelicidin 2 weeks following supplementation; and time taken for overall resolution of illness.

### RESULTS:

**Median (95% CI) time for resolution of severe pneumonia was 30 (29, 31) h in the vitamin D group as compared to 31 (29,33) h in the placebo group** [adjusted hazard ratio (95% CI): 1.39 (1.11, 1.76); P = 0.005]. **The risk of recurrence of pneumonia in next 6 months was comparable in the two groups** [placebo: 36/158 (22.8%); vitamin D: 39/156 (25%); RR (95% CI): 1.13 (0.67,1.90); P 0.69]. Proportion of vitamin D deficient children declined from 38% to 4% in the supplementation group, and from 41% to 33% in the placebo group, two weeks after supplementation. There was no significant effect of vitamin D supplementation on serum levels of cathelicidin, IgA and IgG. The time taken for complete recovery from pneumonia, duration of hospitalization, and fever clearance time were comparable for the two groups. No adverse event was noted related to the intervention.

### CONCLUSION:

**There is no robust evidence of a definite biological benefit, either for therapy or prevention, to suggest a routine megadose supplement of vitamin D3 for under-five children with severe pneumonia.**

Free access: <https://www.indianpediatrics.net/nov2016/967.pdf>

*Ital J Pediatr.* 2016 Dec 7;42(1):106.

### A randomized clinical trial comparing 3 different replacement regimens of vitamin D in clinically asymptomatic pediatrics and adolescents with vitamin D insufficiency.

Talaat IM<sup>1</sup>, Kamal NM<sup>2,3</sup>, Alghamdi HA<sup>3,4</sup>, Alharthi AA<sup>3,5</sup>, Alshahrani MA<sup>6</sup>.

### BACKGROUND:

Pediatric and Adolescent populations both have special needs for vitamin D especially for growing bone. Inadequate vitamin D is defined as 25 (OH) D(25hydroxy vitamin D) < 30 ng/ml.

### METHODS:

We conducted a randomized, controlled clinical trial from July 2014 over 1 year, aiming to assess the changes in 25 (OH) D and biochemical outcome on calcium and PTH(parathyroid hormone) using 3 different regimens of vitamin D replacement. Initial and 4 month 25 (OH) D, calcium, PTH and 12 month 25 (OH) D levels were assayed. Participants divided into 3 groups: 1) given 400 IU daily, 2) given 45000 IU weekly for 2 months then 400 IU daily, 3) given 2000 IU daily for 3 months then 1000 IU daily.

### RESULTS:

The results showed significant difference between the 3 groups as regards 25 (OH) D at 4 and 12 months (P < 0.001). Regimens used in group 2 and 3 caused increase in 25 (OH) D after 4 month (median increase is 225% and 200% respectively). 25 (OH) D dropped in group 1 and 2 (median decrease is 42 and 53% respectively) but continued to increase in group 3 (median change is 6%). In group 2 serum calcium median change was 1.2% with few cases of hypercalcuria. 94.9, 76.1 and 7.7 are the percent of vitamin D deficient participants in groups 1, 2 and 3 respectively after 12 months follow up.

### CONCLUSION:

## Randomised trials in child health in developing countries 2016-17

We advise as a replacement for vitamin D insufficiency, low loading dose with high maintenance dose rather than the opposite to achieve steady increase in serum 25 (OH) D with no hypercalcemic side effects.

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142392/>

[BMC Pregnancy Childbirth](#). 2016 Oct 13;16(1):309.

### **Maternal vitamin D supplementation during pregnancy and lactation to prevent acute respiratory infections in infancy in Dhaka, Bangladesh (MDARI trial): protocol for a prospective cohort study nested within a randomized controlled trial.**

[Morris SK](#)<sup>1,2,3,4</sup>, [Pell LG](#)<sup>5</sup>, [Rahman MZ](#)<sup>6</sup>, [Dimitris MC](#)<sup>5</sup>, [Mahmud A](#)<sup>7</sup>, [Islam MM](#)<sup>8</sup>, [Ahmed T](#)<sup>8</sup>, [Pullenayegum E](#)<sup>9</sup>, [Kashem T](#)<sup>8</sup>, [Shanta SS](#)<sup>8</sup>, [Gubbay J](#)<sup>10,11</sup>, [Papp E](#)<sup>5</sup>, [Science M](#)<sup>10,12</sup>, [Zlotkin S](#)<sup>10,5,9</sup>, [Roth DE](#)<sup>10,5,9</sup>.

#### **BACKGROUND:**

Early infancy is a high-risk period for severe acute respiratory infection (ARI), particularly in low-income countries with resource-limited health systems. Lower respiratory tract infection (LRTI) is commonly preceded by upper respiratory infection (URTI), and often caused by respiratory syncytial virus (RSV), influenza and other common community-acquired viral pathogens. Vitamin D status is a candidate modifiable early-life determinant of the host antiviral immune response and thus may influence the risk of ARI-associated morbidity in high-risk populations.

#### **METHODS/DESIGN:**

In the Maternal Vitamin D for Infant Growth (MDIG) study in Dhaka, Bangladesh ([NCT01924013](#)), **1300 pregnant women are randomized to one of five groups: placebo, 4200 IU/week, 16,800 IU/week, or 28,000 IU/week from 2nd trimester to delivery plus placebo from 0-6 months postpartum; or, 28,000 IU/week prenatal and until 6-months postpartum.** In the Maternal Vitamin D for ARI in Infancy (MDARI) sub-study nested within the MDIG trial, trained personnel conduct weekly postnatal home visits to inquire about ARI symptoms and conduct a standardized clinical assessment. Supplementary home visits between surveillance visits are conducted when caregivers make phone notifications of new infant symptoms. Mid-turbinate nasal swab samples are obtained from infants who meet standardized clinical ARI criteria. Specimens are tested by polymerase chain reaction (PCR) for 8 viruses (influenza A/B, parainfluenza 1/2/3, RSV, adenovirus, and human metapneumovirus), and nasal carriage density of *Streptococcus pneumoniae*. The primary outcome is the incidence rate of microbiologically-positive viral ARI, using incidence rate ratios to estimate between-group differences. **We hypothesize that among infants 0-6 months of age, the incidence of microbiologically-confirmed viral ARI will be significantly lower in infants whose mothers received high-dose prenatal/postpartum vitamin D supplements versus placebo.** Secondary outcomes include incidence of ARI associated with specific pathogens (influenza A or B, RSV), clinical ARI, and density of pneumococcal carriage.

#### **DISCUSSION:**

If shown to reduce the risk of viral ARI in infancy, integration of maternal prenatal/postpartum vitamin D supplementation into antenatal care programs in South Asia may be a feasible primary preventive strategy to reduce the burden of ARI-associated morbidity and mortality in young infants.

## Yaws

[PLoS Negl Trop Dis](#). 2017 Jan 10;11(1):e0005154. doi: 10.1371/journal.pntd.0005154. eCollection 2017 Jan.

### **A Single Dose Oral Azithromycin versus Intramuscular Benzathine Penicillin for the Treatment of Yaws-A Randomized Non Inferiority Trial in Ghana.**

[Kwakye-Maclean C](#)<sup>1</sup>, [Agana N](#)<sup>2</sup>, [Gyapong J](#)<sup>3</sup>, [Nortey P](#)<sup>3</sup>, [Adu-Sarkodie Y](#)<sup>4</sup>, [Aryee E](#)<sup>5</sup>, [Asiedu K](#)<sup>6</sup>, [Ballard R](#)<sup>7</sup>, [Binka F](#)<sup>3</sup>.

#### **BACKGROUND:**

Yaws is a treponemal infection that was almost eradicated fifty years ago; however, the disease has re-emerged in a number of countries including Ghana. A single-dose of intramuscular benzathine penicillin has been the mainstay of treatment for yaws. However, intramuscular injections are painful and pose safety and logistical constraints in the poor areas where yaws occurs. A single center randomized control trial (RCT) carried out in Papua New Guinea in 2012 demonstrated the efficacy of a single-dose of oral azithromycin for the treatment of yaws. In this study, we also compared the efficacy of a single oral dose of azithromycin as an alternative to intramuscular benzathine penicillin for the treatment of the disease in another geographic setting.

#### **METHODOLOGY:**

We conducted an **open-label, randomized non-inferiority trial in three neighboring yaws-endemic districts in Southern Ghana. Children aged 1-15 years with yaws lesions were assigned to receive either 30mg/kg of oral azithromycin or 50,000 units/kg of intramuscular benzathine penicillin. The primary end point was clinical cure rate, defined as a complete or partial resolution of lesions 3 weeks after treatment.** The secondary endpoint was serological cure, defined as at least a 4-fold decline in baseline RPR titre 6 months after treatment. Non-inferiority of azithromycin treatment was determined if the upper bound limit of a 2 sided 95% CI was less than 10%.

#### **FINDINGS:**

The mean age of participants was 9.5 years (S.D.3.1, range: 1-15 years), 247(70%) were males. **The clinical cure rates were 98.2% (95% CI: 96.2-100) in the azithromycin group and 96.9% (95% CI: 94.1-99.6) in the benzathine penicillin group.** The serological cure rates at 6 months were 57.4% (95% CI: 49.9-64.9) in the azithromycin group and 49.1% (95% CI: 41.2-56.9) in the benzathine penicillin group, thus achieving the specified criteria for non-inferiority.

#### **CONCLUSIONS:**

**A single oral dose of azithromycin, at a dosage of 30mg/kg, was non-inferior to a single dose of intramuscular benzathine penicillin for the treatment of early yaws among Ghanaian patients, and provides additional support for the WHO policy for use of oral azithromycin for the eradication of yaws in resource-poor settings.**

Free access: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5224786/>

## Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

[J Trop Pediatr](#). 2017 May 30. doi: 10.1093/tropej/fmx036. [Epub ahead of print]

**Efficacy of Oral Zinc Supplementation in Radiologically Confirmed Pneumonia: Secondary Analysis of a Randomized Controlled Trial.**

[Bagri NK<sup>1</sup>](#), [Bagri N<sup>2</sup>](#), [Jana M<sup>3</sup>](#), [Gupta AK<sup>3</sup>](#), [Wadhwa N<sup>4,5</sup>](#), [Lodha R<sup>1</sup>](#), [Kabra SK<sup>1</sup>](#), [Chandran A<sup>6,7</sup>](#), [Aneja S<sup>8</sup>](#), [Chaturvedi MK<sup>3</sup>](#), [Sodhi J<sup>3</sup>](#), [Fitzwater SP<sup>6</sup>](#), [Chandra J<sup>8</sup>](#), [Rath B<sup>8</sup>](#), [Kainth US<sup>9</sup>](#), [Saini S<sup>3</sup>](#), [Black RE<sup>6</sup>](#), [Santosham M<sup>6,7,10</sup>](#), [Bhatnagar S<sup>3,4</sup>](#).

**Objective:**

To evaluate the effect of zinc as an adjuvant therapy in radiologically confirmed pneumonia in children 2-24 months of age.

**Patients and Methods:**

We analyzed data of 212 children with pneumonia for whom chest X-ray films were available at enrollment and at least two radiologists agreed on the diagnosis of pneumonia. We compared the time to recovery in the two groups (n = 121, zinc group and n = 91, placebo group) using a Cox proportional hazards regression model.

**Results:**

Time to recovery was similar in both groups [median interquartile range: zinc, 84 h (64, 140 h); placebo, 85 h (65, 140 h)]. The absolute risk reduction for treatment failure was 5.2% (95% confidence interval: -4.8, 15.1) with zinc supplementation.

**Conclusion:**

There was no significant beneficial effect of zinc on the duration of recovery or risk of treatment failure in children with radiologically confirmed pneumonia.

[Allergol Immunopathol \(Madr\)](#). 2016 Jul-Aug;44(4):368-75. doi: 10.1016/j.aller.2015.12.006. Epub 2016 May 30.

**Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial.**

[Martinez-Estevez NS<sup>1</sup>](#), [Alvarez-Guevara AN<sup>1</sup>](#), [Rodriguez-Martinez CE<sup>2</sup>](#).

**BACKGROUND:**

Among the preventive strategies for lowering the incidence of upper respiratory tract infections (URTI) and acute diarrhoea episodes, two of the most common diseases in children, zinc supplementation has received special interest. However, there is a need for additional studies that determine the preventive effects of different doses of zinc on URTI and diarrhoeal disease episodes in children.

**METHODS:**

**In a randomised, triple-blind clinical trial, we evaluated the efficacy of 12 months of daily zinc supplementation in the incidence of URTI and acute diarrhoea in a population of healthy children aged between 6 and 12 months living in Bogota, Colombia.** The outcomes analysed were incidence of URTI, acute diarrhoeal disease episodes, and side effects of the interventions.

**RESULTS:**

Between 2010 and 2013, a total of 355 children underwent randomisation, with **174 assigned to the zinc supplementation group and 181 to the control group.** In the multivariate analyses, having been randomised to the non-supplemented control group (IRR 1.73, 95% CI 1.52-1.97, p<0.001), and nursery attendance (IRR 1.41, 95% CI 1.07-1.87, p=0.016) were independently linked to the number of URTI. Likewise, having been randomised to the non-supplemented group (IRR 1.43, 95% CI 1.20-1.71, p<0.001), and lower socioeconomic status (IRR 1.86, 95% CI 1.11-3.13, p=0.018) were independently associated to the number of diarrhoeal disease episodes.

**CONCLUSIONS:**



Daily supplementation of 5mg of zinc during 12 months significantly decreased the incidence of URTI and diarrhoeal disease episodes in a healthy population of children aged between 6 and 12 months.

[J Nutr](#). 2016 Oct;146(10):2058-2066. Epub 2016 Aug 3.

### Comparison of Preventive and Therapeutic Zinc Supplementation in Young Children in Burkina Faso: A Cluster-Randomized, Community-Based Trial.

[Becquey E](#)<sup>1</sup>, [Ouédraogo CT](#)<sup>2</sup>, [Hess SY](#)<sup>3</sup>, [Rouamba N](#)<sup>2</sup>, [Prince L](#)<sup>4</sup>, [Ouédraogo JB](#)<sup>2</sup>, [Vosti SA](#)<sup>4</sup>, [Brown KH](#)<sup>5</sup>.

#### **BACKGROUND:**

The WHO and UNICEF recommend therapeutic zinc supplementation (TZS) for the treatment of diarrhea. In zinc-deficient populations, preventive zinc supplementation might provide greater benefits for reducing diarrhea and malaria incidence and increasing growth and plasma zinc (pZn) concentration. If effective, intermittent preventive zinc supplementation (IPZS) would cost less than daily preventive zinc supplementation (DPZS).

#### **OBJECTIVE:**

We assessed the effects of IPZS, DPZS, and TZS in children on the primary outcomes of diarrhea incidence, malaria incidence, growth, and pZn concentration compared with nonsupplemented control groups.

#### **METHODS:**

Rural Burkinabe children (n = 7641; 6-30 mo old) in 36 clusters were randomly assigned to 1 of 5 treatment groups for 16, 32, or 48 wk: 1) IPZS (10 mg Zn/d for 10 d every 16 wk); 2) DPZS (7 mg Zn/d); 3) TZS (20 mg Zn/d for 10 d for diarrhea); 4) morbidity surveillance control (MSC); or 5) nonintervention control (NIC). Supplemented groups remained masked until completion of primary analyses with mixed models.

#### **RESULTS:**

At baseline, stunting (28.6%) and low pZn concentration (<65 µg/dL; 43.5%) were common. After 48 wk, mean ± SE pZn increased more (P = 0.008) in the DPZS group (3.9 ± 1.3 µg/dL) than in the TZS (-0.5 ± 1.2 µg/dL) and NIC (-1.2 ± 0.9 µg/dL) groups. **All supplemented groups had a moderately lower incidence of reported diarrhea (0.48-0.49 compared with 0.57 episodes/100 d, P = 0.001) and reported fever (1.1-1.2 compared with 1.5 episodes/100d, P < 0.001) and gained slightly less length (3.15-3.20 compared with 3.36 cm/16 wk, P < 0.001) than the MSC group, but did not differ from each other.** Prevalence of diarrhea and incidences of confirmed fever and malaria were not different across study groups.

#### **CONCLUSIONS:**

The preventive and TZS groups had reduced diarrhea incidence, but it is uncertain whether this resulted from a functional response to zinc or reporting bias. The comparison should be re-examined in populations known to respond to zinc supplementation.