

RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

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SEARCH STRATEGY

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Introduction

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

The method of searching for studies to include uses Pubmed, a search engine that is freely available and widely used in most countries throughout the world. The search strategy has been chosen to try to capture as many relevant studies as possible, although it is possible that some are missed. If you know of a relevant RCT 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/entrez/query.fcgi>

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 appropriately performed 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 179 studies were identified. These came from all regions of the world, mostly from developing country researchers. Several trials from 2009-10 will lead to significant changes in child health approaches or clinical recommendations.

We have included the web-link for papers that are freely available in full-text on the Internet. More importantly, through HINARI (<http://www.who.int/hinari/en/>) a program set up by WHO in collaboration with major publishers, the full-text version of over 7000 journal titles are now available to health institutions in 109 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. Previous editions (2002-2008) are available at: www.ichrc.org

Five trials reported significant reductions in mortality (marked with * in the booklet), among these:**

- ❖ In Ethiopia, the mass administration of a single dose of azithromycin (20mg/kg), to control trachoma, resulted in a halving of mortality among children 1-9 years of age, presumably because of an effect on reducing deaths from other common infections causing deaths. For reaching MDG-4 targets, this is arguably the most innovative and practice changing result for the year, and needs to be reproduced in other settings.
- Meta-analysis of RCTs commencing 'Kangaroo Mother Care' in the first week of life in Columbia, India and Ethiopia showed a significant reduction in neonatal mortality [relative risk (RR) 0.49, 95% confidence interval (CI) 0.29-0.82] compared with standard care.
- In India, a large study of community-based women's groups that supported strategies to address maternal and newborn health problems significantly reduced neonatal mortality over a 3 year period. The same effect was not seen in a similar study in Bangladesh

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Some of the other important outcomes from studies in 2009-10 include:

- In South Africa short-term multi-micronutrient supplementation significantly reduced the duration of pneumonia or diarrhea in hospitalised HIV-infected children
- A home stimulation programme taught to caregivers can significantly improve cognitive and motor development in young children infected with HIV, and rehabilitation for children with cerebral malaria can also have a significant benefit on neurocognitive function
- Single dose nevirapine is associated with development of resistance to non-nucleoside reverse transcriptase inhibitor drugs. A short course of AZT plus 3TC, supplementing maternal and infant single-dose nevirapine, reduces resistance mutations in both mothers and infants
- Among HIV-infected women in Tanzania, multivitamins taken in the antenatal period and continued after delivery reduced the risk of low birth weight and infant mortality, but the effect was much stronger for girl babies than boys
- In South Africa and Malawi rotavirus vaccine significantly reduced the incidence of severe rotavirus gastroenteritis during the first year of life
- Insecticide treated bed nets can be coupled with weekly bacterial larvicide distribution in bodies of water to effectively tackle the adult and larval forms of malaria vector
- Having simple screens on doors and windows reduced rates of anaemia in malaria endemic area in Gambia
- Three studies involving eight African countries found that dihydroartemisinin-piperaquine (DP) is as safe and effective as artemether-lumefantrine (AL) in the treatment of uncomplicated falciparum malaria, and 2 of these studies showed lower rates of recurrence at 28 and 42 days with DP, suggesting a longer term prophylactic effect than with AL. DP was also shown to be effective in the treatment of vivax malaria
- In settings where G6PD deficiency is common chlorproguanil-dapsone and its combinations with artesunate, used as intermittent preventative treatment or as treatment for clinical malaria results in a high risk of haemolysis. Three RCTs this year highlighted this complication, and further development of this drug has now ceased
- Delaying BCG vaccination from birth to 10 weeks of age enhances the quantitative and qualitative BCG-specific T cell response, when measured at 1 year of age. In Guinea Bissau mortality was higher among children who received a booster dose of DTP after BCG vaccination
- In India, in the treatment of visceral leishmaniasis a single infusion of liposomal amphotericin B was not inferior to and was less expensive than 15 infusions of amphotericin B deoxycholate over one month

Trevor Duke
July 2010

Acute respiratory infection

(See also Zinc, Pneumococcal vaccine)

Acta Paediatr. 2009 Oct;98(10):1593-9. Epub 2009 Jul 1.

<http://www3.interscience.wiley.com/journal/122477276/abstract?CRETRY=1&SRETRY=0>

Management of bronchiolitis without antibiotics: a multicentre randomized control trial in Bangladesh.

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Abstract

OBJECTIVE: To ascertain that antibiotics have no role in the management of bronchiolitis. **DESIGN:** Multicentre randomized control trial (RCT). **SETTING:** Five purposively selected teaching hospitals in Bangladesh. **PATIENT:** Children under 24 months old with bronchiolitis. **INTERVENTIONS:** **Children were randomized into three groups of therapeutic interventions: parenteral ampicillin (P-Ab), oral erythromycin (O-Ab) and no antibiotic (N-Ab) in adjunct to supportive measures.** **MAIN OUTCOME MEASURES:** Clinical improvement was assessed using 18 symptoms/signs which were graded on a two-point recovery scale of 'rapid' and 'gradual', indicating improvement within 'four days' and 'beyond four days', respectively. **RESULTS:** Each intervention group consisted of 98 +/- 1 children having comparable clinico-epidemiological characteristics at the baseline. The trial revealed that **most chesty features (features appearing to arise from chest, i.e. cough, breathing difficulty, wheeze, chest indrawing, tachypnoea, tachycardia, rhonchi and crepitation) demonstrated a gradual recovery, beyond 4th admission day and, not differing among the three intervention groups** ($p > 0.23$, $p < 0.62$, $p = 0.54$, $p < 0.27$, $p = 0.75$, $p = 0.76$, $p = 0.81$, $p > 0.98$, respectively). **Most non-chesty features (features appearing to arise away from chest, i.e. feeding/sleeping difficulties, social smile, restlessness, inconsolable crying, nasal flaring, fever and hypoxaemia) demonstrated a rapid recovery, within 4 days, remaining comparable among the three intervention groups** ($p < 0.07$, $p = 0.65$, $p = 0.24$, $p < 0.61$, $p = 0.22$, $p = 0.84$, $p = 0.29$ and $p = 0.96$, respectively). However, nasal symptoms (runny nose and nasal blockage) also showed no difference among groups ($p = 0.36$ and $p = 0.66$, respectively). Thus, the dynamics of clinical outcome obviates that children not receiving antibiotics had similar clinical outcome than those who did. **CONCLUSION: In hospital settings, managing bronchiolitis with only supportive measures but without antibiotics remains preferable.**

Comment

This is the second study in a developing country to attempt to differentiate between bronchiolitis and pneumonia in terms of treatment recommendations. An earlier RCT ([PLoS ONE](#), 2008 Apr 23;3(4):e1991) suggested that clinical failure rates were lower in children with non-severe pneumonia and wheeze when given oral amoxicillin. In recent years there have been other large studies from Pakistan and India of non-severe pneumonia showing little difference in response to one antibiotic or another and very low mortality rates, but more than 20% of the study participants had wheeze ([J Trop Pediatr](#), 2008 Dec;54(6):382-9. Epub 2008 Jul 8). In

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these large antibiotic studies a proportion of infants had viral bronchiolitis. It has sometimes been assumed that it is dangerous to not give antibiotics to infants with clinical bronchiolitis, because of the potential for bacterial pneumonia to be missed. This current study explored this issue, but there are some limitations in the reporting of the study which limit how generalisable these results are. The inclusion criteria for this study were: "Any child under two years of age, both male and female, who were hospitalized due to preceding or existing runny nose, cough, breathing difficulty, chest indrawing and rhonchi on auscultation." There was no description of how children with pneumonia were excluded, or how many were screened and excluded. A consort diagram is not included in the study. These were a moderately sick group of children, with 27% having hypoxaemia ($SpO_2 < 90\%$). No deaths were reported, but 5% were referred to a Paediatric Intensive Care for ongoing treatment, withdrawn from the study, and not included in the analyses. Not giving antibiotics to infants with acute viral bronchiolitis in settings where bacterial pneumonia is uncommon and children can be monitored carefully is supported by strong evidence (Spurling GKP, et al. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev 2007; CD005189.). In settings where bacterial pneumonia is very common it will be necessary to validate health workers ability to differentiate on clinical grounds between clinical bronchiolitis and pneumonia, and ensure adequate monitoring and follow-up.

Int J Epidemiol. 2010 Apr;39 Suppl 1:i155-71.

http://ije.oxfordjournals.org/cgi/reprint/39/suppl_1/i155

The effect of case management on childhood pneumonia mortality in developing countries.

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Abstract

BACKGROUND: With the aim of populating the Lives Saved Tool (LiST) with parameters of effectiveness of existing interventions, we conducted a systematic review of the literature assessing the effect of pneumonia case management on mortality from childhood pneumonia.

METHODS: This review covered the following interventions: **community case management with antibiotic treatment, and hospital treatment with antibiotics, oxygen, zinc and vitamin A.** Pneumonia mortality outcomes were sought where available but data were also recorded on secondary outcomes. We summarized results from randomized controlled trials (RCTs), cluster RCTs, quasi-experimental studies and observational studies across outcome measures using standard meta-analysis methods and used a set of standardized rules developed for the purpose of populating the LiST with required parameters, which dealt with the issues of comparability of the studies in a uniform way across a spectrum of childhood conditions.

RESULTS: **We estimate that community case management of pneumonia could result in a 70% reduction in mortality from pneumonia in 0-5-year-old children. In contrast treatment of pneumonia episodes with zinc and vitamin A is ineffective in reducing pneumonia mortality.** There is insufficient evidence to make a quantitative estimate of the

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effect of hospital case management on pneumonia mortality based on the published data. CONCLUSION: The available evidence reinforces the effectiveness of community and hospital case management with World Health Organization-recommended antibiotics and the lack of effect of zinc and vitamin A supportive treatment for children with pneumonia. **Evidence from one trial demonstrates the effectiveness of oxygen therapy but further research is required to give higher quality evidence so that an effect estimate can be incorporated into the LiST model.** We identified no trials that separately evaluated the effectiveness of other supportive care interventions. The summary estimates of effect on pneumonia mortality will inform the LiST model.

Am J Clin Nutr. 2010 Jun;91(6):1667-74. Epub 2010 Apr 7.

<http://www.ajcn.org/cgi/content/full/91/6/1667>

A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2-35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal.

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Abstract

BACKGROUND: Pneumonia is a leading cause of illness and death in young children. Interventions to improve case management of pneumonia are needed. **OBJECTIVE:** Our objective was to **measure the effect of zinc supplementation in children with pneumonia in a population in which zinc deficiency is common.** **DESIGN:** In a double-blind, placebo-controlled clinical trial, children aged 2-35 mo with severe (n = 149) or nonsevere (n = 2479) pneumonia defined according to criteria established by the World Health Organization were randomly assigned to receive zinc (10 mg for children aged 2-11 mo, 20 mg for children aged > or =12 mo) or placebo daily for 14 d as an adjuvant to antibiotics. The primary outcomes were treatment failure, defined as a need for change in antibiotics or hospitalization, and time to recovery from pneumonia. **RESULTS: One of 5 children did not respond adequately to antibiotic treatment; the odds ratios between zinc and placebo groups for treatment failure were 0.95 (95% CI: 0.78, 1.2) for nonsevere pneumonia and 0.97 (95% CI: 0.42, 2.2) for severe pneumonia. There was no difference in time to recovery between zinc and placebo groups for nonsevere (median: 2 d; hazard ratio: 1.0; 95% CI: 0.96, 1.1) or severe (median: 4 d; hazard ratio: 1.1; 95% CI: 0.79, 1.5) pneumonia. Regurgitation or vomiting < or =15 min after supplementation was observed more frequently among children in the zinc group than among those in the placebo group during the supplementation period (37% compared with 13%; odds ratio: 0.25; 95% CI: 0.20, 0.30).** **CONCLUSION:** Adjuvant treatment with zinc neither reduced the risk of treatment failure nor accelerated recovery in episodes of nonsevere or severe pneumonia.

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Int J Epidemiol. 2010 Jun;39(3):795-808. Epub 2010 Feb 15.

Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials.

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Abstract

BACKGROUND: Routine zinc supplementation is a potential intervention for the prevention of acute lower respiratory infection (ALRI) in developing countries. However, discrepant findings from recent randomized trials remain unexplained. **METHODS:** Randomized trials of zinc supplementation in young children in developing countries were identified by a systematic literature review. Trials included in the meta-analysis met specific criteria, including participants <5 years of age, daily/weekly zinc and control supplementation for greater than 3 months, active household surveillance for respiratory morbidity and use of a case definition that included at least one sign of lower respiratory tract illness. ALRI case definitions were classified on the basis of specificity/severity. Incidence rate ratios (IRRs) were pooled by random-effects models. Meta-regression and sub-group analysis were performed to assess potential sources of between-study heterogeneity. **RESULTS:** Ten trials were eligible for inclusion (n = 49 450 children randomized). **Zinc reduced the incidence of ALRI defined by specific clinical criteria [IRR 0.65, 95% confidence interval (CI) 0.52-0.82], but had no effect on lower-specificity ALRI case definitions based on caregiver report (IRR 1.01, 95% CI 0.91-1.12) or World Health Organization 'non-severe pneumonia' (0.96, 95% CI 0.86-1.08). By meta-regression, the effect of zinc was associated with ALRI case definition, but not with mean baseline age, geographic location, nutritional status or zinc dose. CONCLUSIONS: Routine zinc supplementation reduced the incidence of childhood ALRI defined by relatively specific clinical criteria, but the effect was null if lower specificity case definitions were applied.** The choice of ALRI case definition may substantially influence inferences from community trials regarding the efficacy of preventive interventions.

Comment

Zinc prevented ARI that was based on the following case definitions: Fieldworker or physician diagnosis of ALRI based on either a rapid respiratory rate and at least one other observed sign of LRI; or, abnormal sounds on pulmonary auscultation suggestive of pneumonia (bronchial breath sounds and/or crackles/crepitations). Fieldworker or physician diagnosis of ALRIa based on a rapid respiratory rate and at least one additional sign of ALRI and abnormal sounds on pulmonary auscultation suggestive of pneumonia (bronchial breath sounds and/or crackles/crepitations). Zinc didn't seem to prevent ALRI that was diagnosed solely on rapid breathing without auscultatory findings of pneumonia. The different case definitions of the RCTs in zinc may account for the discrepancy of results between settings.

Adolescent health

J Adolesc Health. 2010 Apr;46(4):372-8.

Gender and the effects of an economic empowerment program on attitudes toward sexual risk-taking among AIDS-orphaned adolescent youth in Uganda.

Ssewamala FM, Ismayilova L, McKay M, Sperber E, Bannon W Jr, Alicea S.

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Abstract

PURPOSE: This article examines gender differences in attitudes toward sexual risk-taking behaviors of acquired immune deficiency syndrome (AIDS)-orphaned youth participating in a randomized control trial testing an economic empowerment intervention in rural Uganda. **METHODS:** **Adolescents (average age 13.7 years) who had lost one or both parents to AIDS from 15 comparable schools were randomly assigned to either an experimental (n=135) or a control condition (n=142). Adolescents in the experimental condition, in addition to usual care, also received support and incentives to save money toward secondary education.** **RESULTS:** Findings indicate that although adolescent boys and girls within the experimental condition saved comparable amounts, the intervention appears to have benefited girls, in regard to the attitudes toward sexual risk-taking behavior, in a different way and to a lesser extent than boys. **CONCLUSIONS:** Future research should investigate the possibility that adolescent girls might be able to develop equally large improvements in protective attitudes toward sexual risk taking through additional components that address gendered social norms.

Am J Public Health. 2010 Mar;100(3):483-8. Epub 2010 Jan 14.

Effect of economic assets on sexual risk-taking intentions among orphaned adolescents in Uganda.

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Abstract

OBJECTIVES: We examined the effect of economic assets on sexual risk-taking intentions among school-going AIDS-orphaned adolescents in rural Uganda. **METHODS:** AIDS-orphaned adolescents from 15 comparable schools were randomly assigned to control (n = 133) or treatment (n = 127) conditions. Treatment participants received child savings accounts, workshops, and mentorship. This economic intervention was in addition to the traditional care and support services for school-going orphaned adolescents (counseling and school supplies) provided to both treatment and control groups. Adolescents in the treatment condition were compared with adolescents in the control condition at baseline and at 10 months after the intervention. **RESULTS:** After control for sociodemographic factors, child-caregiver/parental

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communication, and peer pressure, adolescents in the economic intervention group reported a significant reduction in sexual risk-taking intentions compared with adolescents in the control condition. CONCLUSIONS: The findings indicate that in Uganda, a country devastated by poverty and disease (including HIV/AIDS), having access to economic assets plays an important role in influencing adolescents' sexual risk-taking intentions. These findings have implications for the care and support of orphaned adolescents, especially in poor African countries devastated by poverty and sexually transmitted diseases.

Cochrane Database Syst Rev. 2009 Oct 7;(4):CD005215.

<http://mrw.interscience.wiley.com/cochrane/clsystrev/articles/CD005215/frame.html>

Interventions for preventing unintended pregnancies among adolescents.

Oringanje C, Meremikwu MM, Eko H, Esu E, Meremikwu A, Ehiri JE.

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Abstract

BACKGROUND: Unintended pregnancy among adolescents represent an important public health challenge in developed and developing countries. Numerous prevention strategies such as health education, skills-building and improving accessibility to contraceptives have been employed by countries across the world, in an effort to address this problem. However, there is uncertainty regarding the effects of these intervention, and hence the need to review their evidence-base **OBJECTIVES:** To assess the effects of primary prevention interventions (school-based, community/home-based, clinic-based, and faith-based) on unintended pregnancies among adolescents. **SEARCH STRATEGY:** We searched electronic databases (CENTRAL, PubMed, EMBASE) ending December 2008. Cross-referencing, hand-searching, and contacting experts yielded additional citations. **SELECTION CRITERIA:** We included both individual and cluster randomized controlled trials (RCTs) evaluating any interventions that aimed to increase knowledge and attitudes relating to risk of unintended pregnancies, promote delay in the initiation of sexual intercourse and encourage consistent use of birth control methods to reduce unintended pregnancies in adolescents aged 10-19 years. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently assessed trial eligibility and risk of bias in studies that met the inclusion criteria. Where appropriate, binary outcomes were pooled using random effects model with a 95% confidence interval (CI). **MAIN RESULTS:** Forty one RCTs that enrolled 95,662 adolescents were included. Participants were ethnically diverse. Eleven studies randomized individuals, twenty seven randomized clusters (schools (19), classrooms (5), and communities/neighbourhoods (3). Three studies were mixed (individually and cluster randomized). The length of follow up varied from 3 months to 4.5 years. Data could only be pooled for a number of studies (15) because of variations in the reporting of outcomes. Results showed that **multiple interventions (combination of educational and contraceptive interventions) lowered the rate of unintended pregnancy among adolescents.** Evidence on the possible effects of interventions on secondary outcomes (initiation of sexual intercourse, use of birth control methods, abortion, childbirth, sexually transmitted diseases) is not conclusive. Methodological strengths included a relatively large sample size and statistical control for baseline differences, while limitations included lack of biological outcomes, possible self-report bias, analysis neglecting clustered randomization and the use of different statistical

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test in reporting outcomes. **AUTHORS' CONCLUSIONS:** Combination of educational and contraceptive interventions appears to reduce unintended pregnancy among adolescents. Evidence for program effects on biological measures is limited. The variability in study populations, interventions and outcomes of included trials, and the paucity of studies directly comparing different interventions preclude a definitive conclusion regarding which type of intervention is most effective.

Scand J Public Health. 2009 Jun;37 Suppl 2:75-86.

Dating violence among school students in Tanzania and South Africa: prevalence and socio-demographic variations.

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Abstract

AIMS: Widespread adolescent dating violence (DV) in Sub-Saharan Africa calls for immediate action, particularly since it is linked to the spread of HIV/AIDS. This article presents prevalence and demographic correlates of DV among school students in Cape Town and Mankweng (South Africa) and Dar es Salaam (Tanzania). **METHODS:** Data were derived from the baseline data collection of a multi-site randomized controlled trial of an HIV prevention intervention among young adolescents. The results were confined to students who reported previously or currently being in a relationship (n = 6,979). Multiple logistic regression analysis with demographic predictors was employed, controlled for cluster effect. **RESULTS:** Within our sample 10.2%-37.8% had been victims, 3.1%-21.8% had been perpetrators, and 8.6%-42.8% had been both (percentages dependent on site and gender). Before controlling for other factors, religion was a protective factor against violence in Cape Town. After controlling for other factors, a higher age and lower socioeconomic status were associated with belonging to any of the three groups of violence. Being male in all sites was associated with perpetration; being female with victimization (except in Cape Town where the converse finding was obtained). Higher parental education in Cape Town was protective against all types of violence. Ethnicity and living with biological parents were not associated with violence. **CONCLUSIONS:** DV is prevalent and widespread in the study sites. Violence control policies and interventions should target young adolescents. **Since there was not one clearly defined subgroup identified as being at high risk, such programmes should not be limited to high risk groups only.**

Nicotine Tob Res. 2010 Jan;12(1):29-36. Epub 2009 Dec 11.

Tobacco-use psychosocial risk profiles of girls and boys in urban India: implications for gender-specific tobacco intervention development.

Babar AA, Stigler MH, Perry CL, Arora M, Shrivastav R, Reddy KS.

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Abstract

INTRODUCTION: This study examined the distribution of psychosocial risk factors and prevalence of tobacco use among youth in urban India by gender. **METHODS:** Data were obtained from a cross-sectional baseline survey of a group-randomized tobacco intervention trial involving 6th and 8th graders from 32 schools in Delhi and Chennai (N = 11,642). Mixed-effects regression models were used to examine differences in the prevalence of tobacco use by gender, to determine how the relationship between current tobacco use and related psychosocial risk factors varied by gender, to compare the distribution of risk factors by gender, and to determine if any of these relationships varied by grade level or school type. **RESULTS:** 14.7% of girls and 21.1% of boys reported ever-use of tobacco. The psychosocial risk profile for tobacco use was remarkably similar for boys and girls, though some differences were apparent. For example, exposure to advertising and beliefs about social effects of use were significant risk factors for girls but not for boys. Across the board, girls showed lower risk for all psychosocial risk factors, except for perceived prevalence of chewing and smoking, for which girls had higher risk compared with boys. **DISCUSSION:** While the psychosocial risk profile for boys suggests a more vulnerable population for tobacco use, the closing gap in tobacco use between boys and girls indicates a need to examine possible differences in psychosocial risk factors. This study reports that there are subtle, but important, differences in risk factors between genders, having implications for gender-specific intervention development.

Anaemia and iron deficiency

J Nutr. 2010 Jan;140(1):49-53. Epub 2009 Nov 4.

Iron-fortified rice is as efficacious as supplemental iron drops in infants and young children.

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Abstract

How to improve iron status among infants and young children is of continued concern in low- to middle-income countries, including Brazil. In a double blind, 5-mo, home-based, randomized trial in Brazil, we gave one group of mildly anemic 6- to 24-mo-old children (n = 175) rice fortified with micronized ferric pyrophosphate using the Ultra Rice technology and a placebo solution (URG) and another group identical nonfortified rice and iron drops. We instructed parents on the correct dosage of iron drops and to feed their children rice as they normally would. We measured serum ferritin (SF) and hemoglobin (Hb) concentrations at baseline and at 5 mo. At baseline, the prevalences of iron deficiency and anemia in the total sample were 73.1 and 100%, respectively. At 5 mo, SF and Hb increased in both groups, although the change in the URG was larger (P < 0.01). Adult participants were unable to distinguish cooked fortified rice from unfortified rice in terms of smell, color, or taste. As rice is normally consumed at home, MPF-fortified rice increased iron stores and reduced anemia in a group of mildly anemic

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children 6-24 mo old. **In populations where young children are routinely fed approximately 100 g of cooked rice daily, fortifying it with iron may improve iron status at least as well as providing free iron drops.**

J Nutr. 2009 Oct;139(10):1972-9. Epub 2009 Aug 12.

Multiple micronutrients including iron are not more effective than iron alone for improving hemoglobin and iron status of Malian school children.

Ayoya MA, Spiekermann-Brouwer GM, Traoré AK, Stoltzfus RJ, Habicht JP, Garza C.

UNICEF Country Office, New Delhi 110 003, India.

Abstract

Iron deficiency and anemia remain among the most important global public health problems facing school children. Helminth infections often peak at school age and aggravate nutritional risks. We conducted a 12-wk randomized controlled trial in 406 Malian anemic schoolchildren infected with *Schistosoma hematobium* to examine the effects of 2 doses of praziquantel (P) (40 mg/kg body weight), P + 60 mg/d iron (Fe), and/or a multiple micronutrient supplement (MM) that included 18 mg/d Fe. Supplements were administered to the children each school day (5 d/wk) throughout the study. Changes in hemoglobin (Hb), serum ferritin (SF), and serum transferrin receptors (s-TfR) were followed. We also examined interactions between Fe and MM supplements on Hb and SF concentrations and malaria incidence. The effects of Fe on Hb and SF concentrations were greater than the effects of P alone and MM with or without added Fe at 6 and 12 wk ($P < 0.001$). In all groups, s-TfR decreased at 6 and 12 wk compared with baseline. The decrease was most pronounced in the P + Fe group compared with the other 3 groups at wk 6 ($P = 0.05$). Fe and MM interacted negatively at wk 6 and 12 to affect Hb (beta = -0.43, 95% CI = -0.77, -0.09; $P = 0.01$ and beta = -0.47, 95% CI = -0.83, -0.11; $P = 0.01$, respectively) and SF (beta = -0.42, 95% CI = -25.60, 12.31; $P < 0.001$, and beta = -0.37, 95% CI = -0.63, -0.12; $P = 0.004$, respectively). Malaria incidence was higher in the groups treated with added Fe (relative risk: 1.66; 95% CI: 0.75, 3.67). In this context, MM with added iron were not more effective than Fe without MM. Fe supplementation of schoolchildren with 60 mg/d for anemia control should be considered carefully.

J Nutr. 2010 Mar;140(3):635-41. Epub 2010 Jan 27.

In a randomized controlled trial of iron fortification, anthelmintic treatment, and intermittent preventive treatment of malaria for anemia control in Ivorian children, only anthelmintic treatment shows modest benefit.

Rohner F, Zimmermann MB, Amon RJ, Vounatsou P, Tschannen AB, N'goran EK, Nindjin C, Cacou MC, Té-Bonlé MD, Aka H, Sess DE, Utzinger J, Hurrell RF.

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Abstract

Anemia is common among children in sub-Saharan Africa and its etiology is multifactorial. Likely causes of anemia are low bioavailability of dietary iron, malaria, and helminth infection. In this study, we aimed to assess the effect of iron fortification, intermittent preventive treatment (IPT) of malaria, and anthelmintic treatment on hemoglobin concentration and anemia prevalence among school children. The study was a 6-mo, randomized, double-blind, controlled trial enrolling 591 6- to 14-y-old school children in Côte d'Ivoire using the following: 1) iron-fortified biscuits providing an additional 20 mg iron/d as electrolytic iron 4 times/wk; 2) IPT of malaria with sulfadoxine-pyrimethamine at 0 and 3 mo; and 3) anthelmintic treatment at 0 and 3 mo as the interventions. Prevalence of anemia, iron deficiency, malaria parasitemia, and helminth infection was 70.4, 9.3, 57.7, and 54.8%, respectively. Iron fortification did not improve iron status, IPT of malaria did not affect malaria burden, and neither had an impact on anemia prevalence. **Anthelmintics significantly reduced the burden of helminth infections and decreased anemia prevalence (odds ratio: 0.4, 95% CI: 0.3, 0.7).** The low prevalence of iron deficiency and an extended dry season that decreased malaria transmission likely reduced the potential impact of iron fortification and IPT. In this setting, anthelmintic treatment was the only intervention that modestly decreased rates of anemia.

Comment

This study highlights the importance of prevention of anaemia that includes regular treatment of helminths. RCTs in previous years supported the use of albendazole every 4 months in pre-school and school-aged children (Kirwan P, BMC Infect Dis. 2009 Feb 19;9:20). WHO recommends deworming 2 to 3 times per year in areas where the prevalence of geohelminths exceeds 50% (Savioli L, Montresor A, Gyorkos TW, et al. Helminth control in school-age children. A guide for managers of control programs. Geneva: World Health Organization, 2002).

Biomedica. 2009 Jun;29(2):270-81.

<http://www.scielo.org.co/pdf/bio/v29n2/v29n2a12.pdf>

Changes in retinol, hemoglobin and ferritin concentrations in Colombian children with malaria

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Abstract

INTRODUCTION: Malaria, anemia and intestinal parasitism can co-exist in certain populations of Colombian children. The effects of retinol supplementation and anti-intestinal parasite treatment in children with malaria is unknown. Changes after this treatment of with respect to hemoglobin, retinol, ferritin and C reactive protein levels have not been previously monitored. **OBJECTIVE:** The effect of simultaneous intervention with antimalarial, retinol supplementation and anti-intestinal parasites treatment will be monitored by examining levels of hemoglobin,

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ferritin, retinol and C reactive protein in children with malaria. **MATERIALS AND METHODS:** A non-blind experimental study was conducted in 93 children with malaria, aged 4-10 years. Each was randomly allocated to one of the following groups: (1) treatment with antimalarial and retinol supplement (Group MA); (2) treatment with antimalarialretinol supplement and anti-parasitic drug (Group MAP); (3) treatment with antimalarial and antiparasitic drug (Group MP), and (4) treatment only with antimalarials (Group M). The groups were observed for 30 days, with haemoglobin, ferritin, retinol and C reactive protein evaluated on days 0, 8 and 30 after treatment. **RESULTS:** Mean values for the children at day 0 were as follows: hemoglobin 10.3 +/- 1.6 g/dL, retinol 19.1 +/- 6.0 microg/dL, C reactive protein 75 +/- 63 mg/L and ferritin 213 +/- 203 microg/L. On day 30 after treatment, hemoglobin and plasma retinol concentrations increased in 1.4 +/- 1.4 g/dL and 11.5 +/- 8.1 microg/dL, whereas the C reactive protein and ferritin concentrations decreased to 66 +/- 60 mg/L, and 184 +/- 203 microg/L, respectively. No statistically significant differences appeared among the groups. On day 8, significant differences between the groups were observed in hemoglobin concentrations Group MAP was higher when compared to other groups. **CONCLUSION:** On day 30, hemoglobin and retinol were high, whereas C reactive protein was low. Simultaneous administration of a retinol supplement and anti-parasite treatment prevented hemoglobin reduction observed on day 8 without changes in other variables.

J Altern Complement Med. 2010 Feb;16(2):205-11.

Sustainable effect of Ayurvedic formulations in the treatment of nutritional anemia in adolescent students.

Prakash VB, Prakash S, Sharma R, Pal SK.

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Abstract

OBJECTIVES: Anemia is a serious health problem in Indian school children. High prevalence of anemia has been reported in nonpregnant adolescent girls. An investigation was initiated to study the effect of two non-iron-containing Ayurvedic preparations-Sootshekhar Rasa plus Sitopaladi Churna-in improving nutritional anemia among adolescent students. **DESIGN:** This was a single-blinded, randomized, controlled study. **SETTING:** The study setting was Dehradun district, North India. **SUBJECTS:** The subjects comprised a total of 1646 boys and girls, aged 11-18 years, attending school in Dehradun district. **INTERVENTION:** As per World Health Organization guidelines, a total of 1322 adolescent anemic students were randomly divided into 5 groups. Students of group I (control) received starch. Group II, III, and IV students received Sootshekhar Rasa (SR) plus Sitopaladi Churna (SC) in various combinations, namely, SR 125 mg + SC 500 mg daily, SR 250 mg + SC 400 mg daily, and SR 250 mg + SC 400 mg weekly, respectively. Group V student were given iron and folic acid tablet. All the students received treatment for 90 days and were followed up for the next 180 days. **OUTCOME MEASURE:** The outcome measure was to evaluate the effect of Sootshekhar Rasa plus Sitopaladi Churna in improving nutritional anemia. **RESULTS:** The overall prevalence of anemia was found to be 81.3%. At baseline, the mean hemoglobin (Hb) was 97.4 +/- 13.2 g/L and ranged from 96.4 +/- 0.8 g/L to 98.3 +/- 0.8 g/L in various groups. **At end of follow-up (day 270), a significant increase in Hb levels from baseline was observed in all treatment groups; however, the Hb gain (6.9 +/- 0.6 g/L) in group III and group V (3.64 +/- 0.56 g/L) differed significantly from the control group.** A total of 155 students dropped out of the study due to various reasons

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not related to treatment. No adverse side-effect of Ayurvedic medication was noted in any student. CONCLUSIONS: We conclude that a daily dose of Sootshekhar Rasa (250 mg) plus Sitopaladi Churna (400 mg) can produce sustainable improvement of nutritional anemia in adolescent students.

Comment

While this study of Sootshekhar Rasa (or Sutshekhar Ras), Sitopaladi Churna, iron-containing Ayurvedic herbal medication, is likely to be true, these or other Ayurvedic herbal medication has been claimed to be effective treatment for haemachromatosis, hypertension, liver failure, hyperthyroidism, pandemic influenza, Fragile X syndrome and cervical cancer, so claims should be taken in context.

Antibiotics

J Antimicrob Chemother. 2009 Nov;64(5):1096-101. Epub 2009 Sep 16.

<http://jac.oxfordjournals.org/cgi/reprint/64/5/1096>

Efficacy and safety of a single daily dose of gentamicin in hospitalized Indian children: a quasi-randomized trial.

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Abstract

OBJECTIVES: To compare the clinical efficacy, pharmacokinetic profiles and safety of once-daily dosing (ODD) and multiple daily dosing (MDD) of gentamicin in hospitalized Indian children. **PATIENTS AND METHODS:** Four hundred children admitted to our hospital were studied prospectively. The patients were randomized to ODD or MDD groups alternately. The primary outcomes were: (i) a good clinical outcome, as defined; and (ii) occurrence of side effects, if any. Clinical efficacy was determined by comparing the proportion of patients with a favourable response between the two groups, while pharmacokinetic profile was assessed by comparing the peak and trough concentrations of the drug in a subgroup of patients. Safety of the two regimens was compared, besides recording any symptoms due to side effects of the drug, with the help of serum creatinine and brainstem-evoked response audiometry (in a subgroup of the patients). **RESULTS: We found ODD of gentamicin in hospitalized Indian children to be efficacious and safe. A favourable clinical response was achieved in 167 of the 188 patients (89%) in the ODD group and in 161 of the 212 patients (76%) in the MDD group. Similarly, a higher number of patients in the ODD group showed favourable gentamicin peak concentrations as compared with the MDD group (100% versus 87%). The MDD group showed a higher number of trough concentrations in the undesirable range as compared with the ODD group (17% versus 0%).** **CONCLUSIONS:** The study

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supports extended-interval (single daily) dosing in hospitalized Indian children due to its efficacy and safety with the added advantage of needing fewer injections.

Comment

*This further supports previous data provided in an earlier review of RCTs on once-daily doses of gentamicin (<http://tropej.oxfordjournals.org/cgi/reprint/54/5/291?ijkey=j5IAx4yhmc7JeT&keytype=ref>), and other earlier reviews (Miron D. *Pediatr Infect Dis J* 2001; 20: 1169–73.) The daily dose used in this current RCT (6mg/kg) is lower than that currently recommended by WHO (7.5mg/kg in children older than 2 weeks of age: *Pocketbook of Hospital Care for Children* page 338). In this study more than 40% of the children were neonates, and WHO recommends a different dose for babies in the first 2 weeks of life (5mg/kg, or 3mg/kg if low birth weight). In this study the 6mg/kg dose resulted in an average trough level of 1.08mg/L (+/- 0.37), with no trough levels exceeding a dangerous level (2mg/L) among the 22 children receiving daily gentamicin in whom levels were measured. Note that ototoxicity was reported in 1% of children, so this rare complication needs to be considered, even when using the 6mg/kg daily dose. 6mg/kg seems the most appropriate dose of gentamicin for children.*

Anaesthesia and intensive care

Middle East J Anesthesiol. 2009 Oct;20(3):437-42.

ProSeal laryngeal mask airway in infants and toddlers with upper respiratory tract infections: a randomized control trial of spontaneous vs pressure control ventilation.

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Abstract

BACKGROUND: ProSeal LMA (PLMA), one of the advanced supraglottic devices has been successfully used to provide both spontaneous and controlled ventilation in children with upper respiratory tract infection (URTI). URTI does not imply restriction of disease to upper respiratory tract; it has been shown to produce pulmonary dysfunction. PEEP has been shown to improve oxygenation in such cases. This randomized prospective study was designed to compare postoperative adverse events associated with spontaneous respiration (SR) and pressure control ventilation (PCV) with PEEP in infants and toddlers with URTI when using PLMA as an airway device. **METHODS:** In the present study, 90 children, 6 months-2 years, scheduled for infra umbilical surgery were randomized to receive either SR or PCV with PEEP of 5cm H₂O. Patients with risk of aspiration, bronchial asthma, anticipated difficult airway, snoring, passive smoking, morbid obesity, coexisting pulmonary and cardiac disease, lower respiratory tract infection, fever > 38 degrees C and sneezing, were excluded. At emergence, airway secretions, coughing, breath holding, bronchospasm, upper airway obstruction or laryngospasm (LS) were assessed. **RESULTS:** The adverse events were significantly higher in spontaneously

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breathing patients. Score of adverse events was 6.33 +/- 1.6 in PCV and 7.7 +/- 2.2 in SR group (P = 0.001). The mean SpO₂ (%) in PACU was 96.5 +/- 2 in PCV and 94.4 +/- 1.37 in SR (P = 0.000). **CONCLUSION:** Pressure control ventilation with PEEP using PLMA is associated with lower incidence of adverse events in comparison to spontaneous respiration in infants and toddlers with upper respiratory tract infection undergoing infra umbilical surgeries under general anesthesia.

Cleft Palate Craniofac J. 2009 Jul;46(4):368-73. Epub 2008 Nov 20.

Flexible laryngeal mask airway for cleft palate surgery in children: a randomized clinical trial on efficacy and safety.

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Abstract

OBJECTIVE: To evaluate the efficacy of a flexible laryngeal mask airway in children undergoing palatoplasty. **DESIGN:** Prospective, randomized, single-center study. **Setting:** Jawaharlal Institute of Postgraduate Medical Education and Research. **PATIENTS:** Sixty-six children (American Society of Anesthesiologists physical status 1 and 2) scheduled to undergo palatoplasty were assigned randomly to an endotracheal intubation group (RAE group, n = 33) and a flexible laryngeal mask airway group (FLMA group, n = 33). **MAIN OUTCOME MEASURES:** Peak airway pressure, inspired and expired tidal volume, end-tidal carbon dioxide, lung compliance, and airway resistance were continuously measured after placement of the assigned airway. The percentage leak around the airway was quantified as the leak fraction. Parametric data between groups were analyzed using an unpaired Student's t test and within groups using a one-way analysis of variance. Nonparametric variables were analyzed using the Fisher exact test. **RESULTS:** In two children, the flexible laryngeal mask airway was displaced from its original position; whereas, one endotracheal tube advanced endobronchially. The leak fraction was significantly higher in the RAE group when compared with that in FLMA group (13.34% +/- 13.74% versus 5.96% +/- 3.78%, p < .05) until the throat pack was applied. Peak airway pressure and resistance were significantly higher in the RAE group compared with the FLMA group at all time intervals, p < .05. During emergence, frequency of coughing, desaturation, and laryngospasm were increased in the RAE group. **CONCLUSION: A flexible laryngeal airway mask is suitable for maintaining the airway and helps in smooth emergence in children undergoing palatoplasty.**

Anaesth Intensive Care. 2010 May;38(3):530-7.

Effects of clonidine on recovery after sevoflurane anaesthesia in children undergoing cataract surgery.

Ghai B, Ram J, Chauhan S, Wig J.

Randomised trials in child health in developing countries 2009-10

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Abstract

This trial assessed the effects of two doses of clonidine compared with placebo on the quality and speed of recovery in children premedicated with oral midazolam and anaesthetised with sevoflurane for cataract surgery. One hundred and twenty American Society of Anesthesiologists physical status I to II children (aged one to six years), premedicated with oral midazolam 0.5 mg/kg and undergoing elective unilateral cataract surgery with sevoflurane anaesthesia were studied. Children were randomised to intravenous clonidine 1 microg/kg (group C1, n=39), 2 microg/kg (group C2, n=41) or normal saline (group NS, n=40). Clinically successful sub-Tenon local anaesthesia block was required for a patient to be included in the analysis. The primary outcome was the incidence of postoperative agitation. Postoperative agitation was defined as a Pain Discomfort Score of ≥ 3 using items 3 to 5 only, which was assessed 15 minutely until discharge. Agitation was observed in 11/40 (27.5%) children in the NS group compared to 2/39 (5.1%) in group C1 and none in group C2 ($P < 0.001$). Rescue medication to treat severe agitation was required in 5/40 (12.5%) in the NS group, 1/39 (2.6%) in group C1 and none in group C2 ($P = 0.025$). Time to meet discharge criteria was significantly shorter in group C1 compared to the other two groups (48.4 \pm 14.0 minutes compared to C2 79.5 \pm 12.8 minutes and NS 73.1 \pm 20.4 minutes, $P < 0.001$). There were no significant effects on blood pressure and heart rate. Intravenous clonidine 1 microg/kg is effective for reducing agitation after sevoflurane anaesthesia and midazolam premedication in children undergoing cataract surgery. Intravenous clonidine 2 microg/kg was also effective and for a longer period, but was associated with a longer time to discharge.

Paediatr Anaesth. 2010 Feb;20(2):160-7.

A randomized trial of propofol consumption and recovery profile with BIS-guided anesthesia compared to standard practice in children.

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Abstract

AIM: To evaluate the impact of bispectral index (BIS) monitoring on the consumption of propofol and recovery from anesthesia compared to the standard clinical practice in children.
BACKGROUND: Titrating propofol administration using BIS reduces its requirement and shortens the recovery from anesthesia in adults. However, there is still mixed evidence for utility of anesthesia depth monitors in reducing anesthesia requirement in children.
METHODS/MATERIALS: A prospective randomized study was conducted in 50 ASA I children of 2-12 years, randomly assigned into standard practice (SP) or BIS group. After induction with propofol, anesthesia was maintained with 150 microg \times kg⁻¹ \times min⁻¹ propofol infusion. The propofol infusion rate was altered by 20 microg \times kg⁻¹ \times min⁻¹ to maintain the systolic blood pressure within 20% of the baseline (SP group) or BIS value between 45 and 60 (BIS group). The rate of propofol infusion was reduced by 50% about 15 min before the end of surgery. The amount of propofol used and the times from stopping the propofol infusion to eye opening, extubation, response to commands and attaining Steward score of 6 were recorded.

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RESULTS: There was no evidence of a difference in the mean propofol consumption in the two groups (BIS 232.6 +/- 136.7 mg, SP 250.8 +/- 118.2 mg). The intraoperative hemodynamics and BIS values were similar in the two groups. There was no evidence for a difference between groups in the mean times from termination of anesthetic to eye opening, extubation, response to commands and to achieve a Steward Recovery score of 6. **CONCLUSIONS:** Our study showed no benefit of BIS-guided propofol administration on anesthetic consumption or recovery compared to standard anesthetic practice.

Paediatr Anaesth. 2009 Nov;19(11):1090-5.

Epinephrine test dose in children: is it interpretable on ECG monitor?

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Abstract

BACKGROUND: Epidural and other regional blocks are performed in children under general anesthesia; the response to a 'test dose' may be altered during administration of general anesthetics. Limited data is available describing changes in electrocardiogram, blood pressure and heart rate (HR) following unintentional intravascular injection of a lidocaine-epinephrine-containing test dose, under sevoflurane anesthesia in children. **METHODS:** Sixty-eight children undergoing elective surgeries under sevoflurane anesthesia were administered 0.1 ml x kg(-1) of 1% lidocaine with epinephrine 0.5 microg x kg(-1) or normal saline intravenously, to simulate an accidental intravascular test dose. T-wave changes in lead II on the anesthesia monitor and on a printed ECG were noted over the initial 1 min as well as changes in HR and systolic blood pressure (SBP) over an initial 3 min period. **RESULTS:** Following injection of lidocaine-epinephrine, a significant increase in T-wave amplitude in lead II was noted in 91% of children on the ECG monitor and in 94% of children on the ECG printout of the same lead. In 64% of children, an increase in HR of > or =10 b x min(-1) and in 76% of children an increase in SBP of > or =15 mmHg was noted. **CONCLUSION: An increase in T-wave amplitude can easily be detected by carefully observing the ECG monitor or an ECG printout within a minute following the accidental i.v. administration of 0.1 ml x kg(-1) of 1% lidocaine-epinephrine (0.5 microg x kg(-1)) regional anesthetic test dose in children under sevoflurane anesthesia.**

J Crit Care. 2010 Mar;25(1):56-61. Epub 2009 Jul 9.

Effect of frequency of ventilator circuit changes (3 vs 7 days) on the rate of ventilator-associated pneumonia in PICU.

Samransamruajkit R, Jirapaiboonsuk S, Siritantiwat S, Tungsrjitdee O, Deerojanawong J, Sritippayawan S, Prapphal N.

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Abstract

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PURPOSE: Ventilator-associated pneumonia (VAP) is associated with significant morbidity and mortality in pediatric intensive care unit (PICU). Our purpose was to evaluate the effects of ventilator circuit change on the rate of VAP in the PICU. **METHODS:** A prospective randomized controlled trial was conducted at a university hospital PICU. Children (younger than 18 years) who received mechanical ventilation from December 2006 to November 2007 were randomly assigned to receive ventilator circuit changes every 3 or 7 days. **RESULTS:** Of 176 patients, 88 were assigned to receive ventilator circuit every 3 days and 88 patients had a change weekly. The rate of VAP was 13.9/1000 ventilator days for the 3-day circuit change (n = 12) vs 11.5/1000 ventilator days (n = 10) for the 7-day circuit change (odds ratio, 0.8; confidence interval, 0.3-1.9; P = .6). There was a trend toward decreased PICU stay and mortality rate in 7-day change group compared to 3-day change group but did not reach statistical significance. Furthermore, switching from a 3-day to a 7-day change policy could save costs up to US \$22,000/y. **CONCLUSIONS:** The 7-day ventilator circuit change did not contribute to increased rates of VAP in our PICU. Thus, it may be used as a guide to save workload and supply costs.

Asthma

J Med Assoc Thai. 2010 May;93(5):541-9.

Ketotifen versus inhaled budesonide for controlling childhood asthma.

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Abstract

BACKGROUND: International asthma guideline recommends inhaled corticosteroids therapy for children of all ages as the first controller. However, in some less developed parts of the world, ketotifen, an old inexpensive medicine with antihistaminic and anti-allergic reactions, has been found to be the most favored prophylactic agents. **OBJECTIVE:** To compare the efficacy and safety of ketotifen and inhaled budesonide in asthmatic children aged 8 months to 14 years at Banpong Hospital, located 80 km south from Bangkok. **MATERIAL AND METHOD:** Children who had been admitted with acute asthmatic attack in 2008 at Banpong Hospital and had > 3 episodes of wheeze with good response to nebulized bronchodilators were randomized into two groups. Ketotifen group (n = 16) were given oral ketotifen 0.5 mg or 1 mg twice daily depending on age. Budesonide group (n = 14) were given as inhaled budesonide 200 microg (MDI) twice daily. Caregivers recorded children's asthmatic symptoms and nebulized treatments in diaries every day. The enrolled children received these two treatment regimens and were followed up for 26 weeks. **RESULTS:** Number of ER visits decreased significantly after both treatments (p < 0.005). The percentage of children with reduction in ER visits was comparable between ketotifen and budesonide (p = 0.16). Ketotifen group also demonstrated a reduction in days of hospital stay (p < 0.05). Budesonide treatment resulted in more symptom-free days (p < 0.05). Both medications were well tolerated and safe. The only demonstrated side effect of ketotifen was weight gain. The growth rate in height for both groups did not differ. **CONCLUSION: Both ketotifen and inhaled budesonide are effective, safe, and well-**

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tolerated in the prevention of asthma exacerbation in children particularly in the country with limited resource.

Comment

There is a Cochrane review on the use of ketotifen, an inexpensive antihistamine, in asthma in children (<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001384/frame.html>). This included 26 trials and 1826 participants. This review showed a benefit of ketotifen in mild to moderate asthma, in more children being able to cease bronchodilator therapy (salbutamol etc) after 12-16 weeks of ketotifen treatment than in the placebo groups. However there were some side effects of ketotifen: sedation (21%), weight gain (27%), compared with the placebo group (12% and 17% respectively). The value of using ketotifen for asthma control in any given child needs to be weighed (a) against the side effects and their impact on daily activities, learning and development, and (b) the availability of other preventative therapies.

Indian J Pediatr. 2009 Nov;76(11):1131-5.

Levosalbutamol vs racemic salbutamol in the treatment of acute exacerbation of asthma.

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Abstract

OBJECTIVE: To compare efficacy and tolerability of levosalbutamol (Group 1) and racemic salbutamol (Group 2) for the treatment of acute exacerbation of asthma in children age 5 to 18 yr. **METHODS:** A randomized double blind clinical study involving 60 children was undertaken between October' 06 to December' 07. **RESULTS:** The following baseline clinical characteristics were recorded initially and after giving 3 nebulizations at 20 min intervals in the 1st hour of presentation viz respiratory rate (RR), heart rate (HR), oxygen saturation in room air SPO₂, PEFR (peak expiratory flow rate), serum K⁺ level and asthma score. In Group 1 patients (levosalbutamol), there was significant increment in SPO₂ and PEFR (P<0.05) values with decrease in tachypnea and asthma score while no significant difference was found in pre and post treatment HR & Serum K⁺ levels. In Group 2 patients although there was clinical improvement in terms of SPO₂, PEFR, RR and asthma score, it resulted in significant tachycardia and decrease in K⁺ levels. **CONCLUSION:** Levosalbutamol appears to be more efficacious than racemic salbutamol in terms of improvement in PEFR, SPO₂ and asthma score while deleterious effects of tachycardia and fall in serum K⁺ were seen with racemic salbutamol.

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J Asthma. 2009 Nov;46(9):906-10.

Effectiveness of asthma education with and without a self-management plan in hospitalized children.

Espinoza-Palma T, Zamorano A, Arancibia F, Bustos MF, Silva MJ, Cardenas C, De La Barra P, Puente V, Cerda J, Castro-Rodriguez JA, Prado F.

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Abstract

Background. Formal education in primary care can reduce asthma exacerbations. However, there are few studies in hospitalized children, with none originating in Latin America. **Methods.** A prospective randomized study was designed to evaluate whether a full education with self-management plan (ESM) was more effective than an education without self-management plan (E) in reducing asthma hospitalization. Children (5 to 15 years of age) who were hospitalized for an asthma attack were divided in two groups. Children in the E group received general instructions based on a booklet. Those in the ESM group received the same booklet plus a self-management guide and a puzzle game that reinforces the lessons learned in the booklet. Patients were interviewed every 3 months, by telephone, for one year. Interviewers recording the number of hospitalizations, exacerbations, and emergency visits for asthma and oral steroid burst uses. **Results.** From 88 children who met the inclusion criteria, 77 (86%) completed one year of follow-up (41 from E and 36 from ESM group). Overall, after one year, the hospitalization decreased by 66% and the inhaled corticosteroids therapy increased from 36% to 79%. At the end of the study, there was no difference in exacerbations, emergency visits, oral steroid burst uses, or hospitalizations between the two groups. **Conclusions.** **Asthma education with or without a self-management plan during asthma hospitalization were effective in reducing exacerbations, emergency visits, oral steroid burst uses, and future rehospitalizations. This evidence supports the importance of providing a complete asthma education plan in any patient who is admitted for asthma exacerbation.**

Cardiology

BMJ. 2010 Jun 7;340:c2641. doi: 10.1136/bmj.c2641.

http://www.bmj.com/cgi/reprint/340/jun07_1/c2641

Community based lifestyle intervention for blood pressure reduction in children and young adults in developing country: cluster randomised controlled trial.

Jafar TH, Islam M, Hatcher J, Hashmi S, Bux R, Khan A, Poulter N, Badruddin S, Chaturvedi N; Hypertension Research Group.

Jafary F, Hameed A, Khan A, Gilani A, Zaidi S, Syed N, Jessani S, Qadri Z, Cosgrove P.

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Abstract

OBJECTIVE: To assess the effectiveness of a community based lifestyle intervention on blood pressure in children and young adults in a developing country setting. **DESIGN:** Cluster randomised controlled trial. **SETTING:** 12 randomly selected geographical census based clusters in Karachi, Pakistan. **PARTICIPANTS:** 4023 people aged 5-39 years. **INTERVENTION:** Three monthly family based home health education delivered by lay health workers. **MAIN OUTCOME MEASURE:** Change in blood pressure from randomisation to end of follow-up at 2 years. **RESULTS:** Analysed using the intention to treat principle, the change in systolic blood pressure (adjusted for age, sex, and baseline blood pressure) was significant; it increased by 1.5 (95% confidence interval 1.1 to 1.9) mm Hg in the control group and by 0.1 (-0.3 to 0.5) mm Hg in the home health education group (P for difference between groups=0.02). Findings for diastolic blood pressure were similar; the change was 1.5 mm Hg greater in the control group than in the intervention group (P=0.002). **CONCLUSIONS:** Simple, family based home health education delivered by trained lay health workers significantly ameliorated the usual increase in blood pressure with age in children and young adults in the general population of Pakistan, a low income developing country. This strategy is potentially feasible for up-scaling within the existing healthcare systems of Indo-Asia.

Community health services

BMC Public Health. 2009 Aug 3;9:279.

<http://www.biomedcentral.com/1471-2458/9/279>

The EPICS Trial: Enabling Parents to Increase Child Survival through the introduction of community-based health interventions in rural Guinea Bissau.

Mann V, Fazzio I, King R, Walker P, dos Santos A, de Sa JC, Jayanti C, Frost C, Elbourne D, Boone P.

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Abstract

BACKGROUND: Guinea-Bissau is a small country in West Africa with a population of 1.7 million. The WHO and UNICEF reported an under-five child mortality of 203 per 1000, the 10th highest amongst 192 countries. The aim of the trial is to assess whether an intervention package that includes community health promotion campaign and education through health clubs, intensive training and mentoring of village health workers to diagnose and provide first-line treatment for children's diseases within the community, and improved outreach services can generate a rapid and cost-effective reduction in under-five child mortality in rural regions of Guinea-Bissau. Effective Intervention plans to expand the project to a much larger region if there is good evidence after two and a half years that the project is generating a cost-effective,

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sustainable reduction in child mortality. METHODS/DESIGN: This trial is a cluster-randomised controlled trial involving 146 clusters. The trial will run for 2.5 years. The interventions will be introduced in two stages: seventy-three clusters will receive the interventions at the start of the project, and seventy-three control clusters will receive the interventions 2.5 years after the first clusters have received all interventions if the research shows that the interventions are effective. The impact of the interventions and cost-effectiveness will be measured during the first stage. The package of interventions includes a community health promotion campaign and education through health clubs, and intensive training and mentoring of village health workers to diagnose and provide first-line treatment for common children's diseases within the community. It also includes improved outreach services to encourage provision of antenatal and post natal care and provide ongoing monitoring for village health workers. The primary outcome of the trial will be the proportion of children that die under 5 years of age during the trial. Secondary outcomes will include age at and cause of child deaths, neonatal mortality, infant mortality, maternal mortality, health knowledge, health seeking behaviour, morbidity and costs. DISCUSSION: The trial will be run by research and service delivery teams that act independently, overseen by a trial steering committee. A data monitoring committee will be appointed to monitor the outcome and any adverse effects. TRIAL REGISTRATION: Current Controlled Trials ISRCTN52433336.

Health Psychol. 2009 Jul;28(4):493-500.

An intervention to reduce kerosene-related burns and poisonings in low-income South African communities.

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Abstract

OBJECTIVE: Unintentional injury rates in low- and middle-income countries are up to 50 times higher than high-income nations. In South Africa, kerosene (paraffin) is a leading cause of poisoning and burns, particularly in low-income communities where it serves as a primary fuel for light, cooking, and heating. This study tested a community-based intervention to reduce kerosene-related injury risk. The intervention used a **train-the-trainers model, whereby expert trainers train local paraprofessionals, who in turn deliver educational materials to community residents.** The intervention was theory-driven, pragmatically motivated, and culturally sensitive. **DESIGN:** Prospective quasi-experimental intervention design with nonequivalent case versus control groups. **MAIN OUTCOME MEASURES:** Three primary outcome measures were considered: self-reported knowledge of kerosene safety, observed practice of safe kerosene use, and self-reported recognition of risk for kerosene-related injury. **RESULTS:** ANOVA models suggest **a large and significant increase in self-reported kerosene-related knowledge in the intervention community compared to the control community. There were smaller, but statistically significant changes, in kerosene-related safety practices and recognition of kerosene injury risk in the intervention community compared to the control community.** **CONCLUSION:** The intervention was successful. A train-the-trainers model might be an effective educational tool to reduce kerosene-related injury risk in low-income communities within low- and middle-income countries.

Development and mental health

Dev Med Child Neurol. 2010 Jun;52(6):547-51. Epub 2009 Nov 28.

The effect of a basic home stimulation programme on the development of young children infected with HIV.

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Abstract

AIMS: The human immunodeficiency virus (HIV) potentially causes a significant encephalopathy and resultant developmental delay in infected children. The aim of this study was to determine whether a home-based intervention programme could have an impact on the neurodevelopmental status of children infected with HIV. **METHOD:** A longitudinal, randomized, controlled trial was conducted. A total of 122 children aged less than 2 years 6 months were assigned to either a comparison or an experimental group. Children in the experimental group were given a home stimulation programme that was updated every 3 months. The home programme included activities to promote motor, cognitive, and speech and language development. Children in the comparison group received no developmental intervention. Children were assessed by a blinded assessor at baseline, 6 months, and 12 months using the Bayley Scales of Infant Development, 2nd edition. **RESULTS:** The children in this study came from poor socioeconomic backgrounds and their nutritional status was suboptimal. The experimental group included 60 children (30 males, 30 females) with a mean age of 18 months (SD 8.1 mo). The comparison group included 62 children (32 males, 30 females) with a mean age 19 months (SD 8.2 mo). Cognitive and motor development were severely affected at baseline, with 52% of the children having severe cognitive delay and 72% having severe motor delay at baseline. Children in the experimental group showed significantly greater improvement in cognitive ($p=0.010$) and motor ($p=0.020$) development over time than children in the comparison group. **INTERPRETATION:** A home stimulation programme taught to the caregiver can significantly improve cognitive and motor development in young children infected with HIV.

Comment

This study clearly shows that children with HIV are at very high risk of developmental delay. This was an impoverished population, with only one third of families living in their own houses, one third of caregivers had completed school, and 18 children died during the study period. Only 16 were on HAART at the beginning of the study. The intervention included stimulation based on activities of daily living, such as bathing, feeding, dressing, and playing. Caregivers were given a picture book to show their child each day, and talk about what they saw in the book. The study showed that a basic home stimulation programme can improve developmental outcome, and that HIV-positive children require long-term follow-up of developmental status.

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J Dev Behav Pediatr. 2009 Aug;30(4):310-8.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2747354/?tool=pubmed>

Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors.

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Abstract

OBJECTIVE: Our earlier studies on Ugandan children surviving cerebral malaria showed cognitive deficits mainly in attention and memory. We now present the first study in sub-Saharan Africa to investigate the feasibility and potential benefits of computerized cognitive rehabilitation training on neuropsychological and behavioral functioning of children surviving cerebral malaria. **METHODS:** A randomized trial in which 65 children admitted 45 months earlier with cerebral malaria were recruited at Mulago Hospital, Kampala, Uganda. For 8 weeks, 32 of the children received weekly training sessions using Captain's Log cognitive training software and the other 33 were assigned to a nontreatment condition. Pre- and postintervention assessments were completed using CogState, a computerized neuropsychological battery, measuring visuomotor processing speed, working memory, learning, attention and psychomotor speed and the Child Behavior Checklist measuring internalizing problems, externalizing problems, and total problems. **RESULTS:** Preintervention scores were similar between both groups. Treatment effects were observed on visuospatial processing speed [group effect (standard error) 0.14 (0.03); $p < .001$], on a working memory and learning task [0.08 (0.02); $p < .001$], psychomotor speed [0.14 (0.07); $p = .04$], and on internalizing problems [-3.80 (1.56); $p = .02$] after controlling for age, sex, school grade, quality of the home environment, and weight for age z scores. Similar treatment effects were observed when no adjustments for the above covariates were made. **CONCLUSIONS:** **Computerized cognitive training long after the cerebral malaria episode has immediate benefit on some neuropsychological and behavioral functions in African children. The long-term benefit of this intervention needs to be investigated.**

Comment

The computerized cognitive rehabilitation training package used was a commercial one (costing many thousands of dollars) "consisting of 35 multi-level brain-training exercises designed to help develop and remediate a wide range of cognitive skills". It is not surprising that if children are trained in such computer-based tools they will be better at doing computer-based cognitive tests, which was how the outcomes were measured. Therefore the link between the the intervention and the outcome measure is not entirely independent. However this study does show the value of early measures to improve cognition in children with acquired brain injury. The study also suggests that there is a large burden of secondarily preventable brain injury among children who don't receive any education stimulation after cerebral malaria. There is a need to finding inexpensive and effective ways to reproduce this.

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Child Abuse Negl. 2010 Mar;34(3):206-13. Epub 2010 Mar 5.

Primary prevention of parent-child conflict and abuse in Iranian mothers: a randomized-controlled trial.

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Abstract

OBJECTIVE: The aim of this study was to assess whether primary health care settings can be used to engage and provide a preventive intervention to mothers of young children. **METHODS:** Two hundred and twenty-four mothers who had come to the health centers were randomly assigned to either control group (CG: n=116) or intervention group (IG: n=108). Mothers in IG were taught about the role of parenting skills in families and common mistakes in parenting in 2-h-weekly sessions for 2 successive weeks. A parenting questionnaire was distributed to mothers at pre-test and after 8 weeks from the last training session. **RESULTS:** Compared to the CG, there were significant improvements from pre- to post-test in IG on measures of Parenting Scales (PS) total scores and Parent-Child Conflict Tactics Scale-modified (CTSPCm) total scores. This improvement was maintained at 8-week follow up. **CONCLUSION:** The results support previous international studies that primary health care settings can be used successfully to engage and provide preventive interventions to mothers of young children. **PRACTICE IMPLICATIONS:** Within health centers of Iran where parents routinely bring their children for monitoring of growth or vaccinating against some disease, mothers with a child aged between 2 and 6 years received a parent training. The program gave skills for managing misbehavior and preventing child behavior problems. Mothers reported that their behaviors improved from pre-treatment to post-treatment measured at 8-week follow up. The current work may lead decision-makers to organize this program for all of the health centers to train Iranian mothers.

J Adv Nurs. 2009 Dec;65(12):2552-61.

<http://www3.interscience.wiley.com/cgi-bin/fulltext/122686587/PDFSTART>

Reducing burnout in mothers with an intellectually disabled child: an education programme.

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Abstract

AIM: This paper is a report of a study conducted to examine the effect of participating in an education program on burnout for mothers of children with an intellectual disability. **BACKGROUND:** Mothers with an intellectually disabled child are prone to suffer from excessive stress and burnout. There is limited evidence for the effectiveness of education interventions aimed at reducing burnout levels in this population. **METHODS:** After baseline screening, mothers who agreed to participate (n = 90) were randomized to an intervention or control group. The intervention group participated in an interactive education programme for 1 hour, in addition to using an educational booklet designed and presented by the researchers. The booklet contained information about the characteristics of intellectually disabled children, the

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specific health care and education they require, non-profit organizations and foundations providing assistance, and ways in which mothers can cope with stress. The control group received the same intervention separately after completing the post-test. The study was carried out from 2004 to 2005. **FINDINGS:** Intervention group members reported fewer episodes of emotional burnout compared to the control group, indicating that participation in a nursing education programme reduced the level of burnout experienced by mothers who have an intellectually disabled child. There were no effects of the education programme on perceptions of personal success, i.e. mother's feelings of competence and successful achievement in care of their intellectually disabled child. **CONCLUSION:** Nurse-administered education should be provided for mothers who have an intellectually disabled child in order to reduce the degree of emotional burnout that these mothers typically experience.

J Altern Complement Med. 2009 Dec;15(12):1355-61.

Effects of Thai traditional massage on autistic children's behavior.

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Abstract

OBJECTIVES: The objective of this study was to assess whether there were any therapeutic effects of Thai Traditional Massage (TTM) on major behavioral and emotional disturbances in Thai autistic children. **DESIGN:** This was a randomized controlled trial study. **Settings/location:** The study was conducted at the Rehabilitation Centre of the Thai Red Cross Society. **SUBJECTS:** A total of 60 autistic children between the ages of 3 and 10 completed this study. **Interventions:** Standard sensory integration therapy (SI) was compared to the SI with TTM treatments. **Outcome measures:** Parents and teachers assessed major behavior disturbances using the Conners' Rating Scales at 0 and 8 weeks. Sleep Diary (SD), recorded by the parents, assessed the patient's sleeping patterns every week. **RESULTS:** Sixty (60) autistic children, mean age 4.67 +/- 1.82, were recruited. No statistical differences were seen in the demographic and baseline data among both groups. From both the Conners' Teacher Questionnaire and SD, statistical improvement was detected for conduct problem, hyperactivity, inattention-passivity, hyperactivity index, and sleeping behavior. However, results from the Conners' Parent Questionnaire revealed an improvement only for anxiety ($p = 0.04$) in the massage group, whereas when both groups were compared, a significant improvement in conduct problem ($p = 0.03$) and anxiety ($p = 0.01$) was found. Results indicated that TTM may have a positive effect in improving stereotypical behaviors in autistic children. **CONCLUSIONS:** Over a period of 8 weeks, our findings suggested that TTM could be used as a complementary therapy for autistic children in Thailand.

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Am J Clin Hypn. 2009 Jul;52(1):23-34.

A spiritual-hypnosis assisted treatment of children with PTSD after the 2002 Bali terrorist attack.

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Abstract

The aim of this study was to assess the effectiveness of a spiritual-hypnosis assisted therapy (SHAT) for treatment of posttraumatic stress disorder (PTSD) in children. All children, age 6-12 years (N=226; 52.7% females), who experienced the terrorist bomb blasts in Bali in 2002, and subsequently were diagnosed with PTSD were studied, through a longitudinal, quasi-experimental (pre-post test), single-blind, randomized control design. Of them, 48 received group SHAT (treatment group), and 178 did not receive any therapy (control group). Statistically significant results showed that SHAT produced a 77.1% improvement rate, at a two-year follow up, compared to 24% in the control group, while at the same time, the mean PTSD symptom score differences were significantly lower in the former group. We conclude that the method of spiritual-hypnosis is highly effective, economic, and easily implemented, and has a potential for therapy of PTSD in other cultures or other catastrophic life-threatening events.

Psychother Psychosom. 2009;78(6):364-71. Epub 2009 Sep 8.

School-based intervention for the treatment of tsunami-related distress in children: a quasi-randomized controlled trial.

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Abstract

BACKGROUND: On December 26, 2004, a tsunami hit the southern coast of Sri Lanka, leaving thousands dead and injured. Previous research has found significant mental health problems among children exposed to major disasters. School-based universal interventions have shown promise in alleviating distress and posttraumatic symptomatology in children and adolescents. This study evaluated the efficacy of a school-based intervention in reducing stress-related symptomatology among Sri Lankan children exposed to the tsunami. **METHODS:** In a quasi-randomized controlled trial 166 elementary school students (ages 9-15) with significant levels of tsunami exposure and previous traumatic background were randomly assigned to a 12-session structured program 'ERASE Stress Sri Lanka' (ES-SL) or to a waiting list (WL) religious class control group. Students were assessed 1 week prior and 3 months after the intervention on measures of posttraumatic symptomatology [including posttraumatic stress disorder (PTSD) and severity of posttraumatic symptomatology], depression, functional problems, somatic problems and hope. **RESULTS:** This study shows a significant reduction on all outcome variables. PTSD severity, functional problems, somatic complaints, depression and hope scores were all significantly improved in the ES-SL group compared to the WL group. No new cases of PTSD

Randomised trials in child health in developing countries 2009-10

were observed in the experimental group. **CONCLUSION:** This study adds to the growing body of evidence suggesting the efficacy of school-based universal approaches in helping children in regions touched by war, terror and disaster and suggests the need to adopt a two-stage approach toward dealing with trauma-exposed students, namely, starting with a universal intervention followed by targeted specialized interventions for those still suffering from posttraumatic distress.

Psychother Psychosom. 2009;78(5):298-306. Epub 2009 Jul 24.

Narrative exposure therapy versus interpersonal psychotherapy. A pilot randomized controlled trial with Rwandan genocide orphans.

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Abstract

BACKGROUND: The aim of the present study was to evaluate the efficacy of treatment modules for trauma spectrum disorders in a sample of Rwandan genocide orphans. **METHODS:** Twenty-six orphans (originally 27) who presented with posttraumatic stress disorder (PTSD) at first assessment continued to meet a PTSD DSM-IV diagnosis 6 months after their initial assessment. They were offered participation in a controlled treatment trial. A group adaptation of interpersonal psychotherapy (IPT, $n = 14$) was compared to individual narrative exposure therapy (NET, $n = 12$). The last NET session involved guided mourning. Each treatment program consisted of 4 weekly sessions. Main outcome measures were diagnostic status and symptoms of PTSD and depression assessed before treatment, at 3 months post-test and at 6 months follow-up using the Clinician-Administered PTSD Scale, Mini-International Neuropsychiatric Interview, and Hamilton Rating Scale. **RESULTS:** At post-test, there were no significant group differences between NET and IPT on any of the examined outcome measures. At 6-month follow-up, only 25% of NET, but 71% of IPT participants still fulfilled PTSD criteria. There was a significant time x treatment interaction in the severity of PTSD [Wilks' Lambda = 0.75, $F(2,23) = 3.93$; $p < 0.05$] and depression symptoms [Wilks' Lambda = 0.23, $F(2,23) = 3.40$; $p = 0.05$]. At follow-up, NET participants were significantly more improved than IPT participants with respect to both the severity of symptoms of PTSD and depression. **CONCLUSIONS:** Individual NET in combination with group-based mourning comprises an effective treatment for traumatized survivors who have to bear the loss of loved ones and have been suffering from symptoms of PTSD and depression.

Diarrhoea

(see also HIV, Hygiene)

Indian Pediatr. 2010 Apr 7;47(4):309-15. Epub 2009 May 20.

<http://indianpediatrics.net/apr2010/309.pdf>

Single dose azithromycin versus ciprofloxacin for cholera in children: a randomized controlled trial.

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Abstract

OBJECTIVE: To compare the clinical and bacteriological success of single dose treatment with azithromycin and ciprofloxacin in children with cholera. **DESIGN:** Randomized, open labelled, clinical controlled trial. **SETTING:** Tertiary care hospital. **PARTICIPANTS:** 180 children between 2-12 years, having watery diarrhea for ≤ 24 hr and severe dehydration, who tested positive for *Vibrio cholerae* by hanging drop examination or culture of stool. **INTERVENTION:** Azithromycin 20 mg/kg single dose (n=91) or Ciprofloxacin 20 mg/kg single dose (n=89). Dehydration was managed according to WHO guidelines. **MAIN OUTCOME MEASURES:** Clinical success (resolution of diarrhea within 24 hr) and bacteriological success (cessation of excretion of *Vibrio cholerae* by day 3). Secondary outcome variables included duration of diarrhea, duration of excretion of *Vibrio cholerae* in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse. **RESULTS:** The rate of clinical success was 94.5% (86/91) in children treated with Azithromycin and 70.7% (63/89) in those treated with Ciprofloxacin [RR (95% CI)=1.34 (1.16-1.54); P< 0.001]. Bacteriological success was documented in 100% (91/91) children in Azithromycin group compared to 95.5% (85/89) in Ciprofloxacin group [RR (95% CI)=1.05 (1.00 -1.10); P=0.06]. **Patients treated with Azithromycin had a shorter duration of diarrhea [mean(SD) 54.6 (18.6) vs 71.5 (29.6) h; mean difference (95% CI) 16.9 (9.6 -24.2); P<0.001] and lesser duration of excretion of *Vibrio cholerae* [mean(SD) 34.6 (16.3) vs 52.1 (29.2) h; mean difference (95% CI) 17.5 (0.2 -24.7), P<0.001] in children treated with Azithromycin vs Ciprofloxacin. The amount of intravenous fluid requirement was significantly less among subjects who received Azithromycin as compared to those who received Ciprofloxacin [mean(SD) 4704.7(2188.4) vs 3491.1(1520.5) mL; Mean difference (95% CI) 1213(645.3 - 1781.9); P<0.001].** Proportion of children with bacteriological relapse was comparable in two groups [6.7% (6/89) vs 2.2% (2/91); RR (95% CI) 0.95 (0.89 -1.01); P=0.16]. None of the children in either group had a clinical relapse. **CONCLUSION: Single dose azithromycin is superior to ciprofloxacin for treating cholera in children.**

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Comment

Azithromycin is an effective antimicrobial treatment for cholera. A flaw in this otherwise well conducted study is the absence of blinding, which opens the study to criticism that could be avoided if the outcome assessors were blinded to the treatment group. Also, the azithromycin was supplied free by the drug company. This study adds to the other RCTs on the use of azithromycin this year: for trachoma (See Ophthalmology section) and malaria (see Malaria section).

Water purification

This year trials of water purification involved sand filtration, sodium dichloroisocyanurate, solar disinfection, and a straw filter that is used to suck up drinking water. All methods decreased coliform counts in drinking water, but only sand filtration and the personal drinking straw were reported to be associated with lower prevalence of diarrhoea. The two measures requiring compliance (solar disinfection and the LifeStraw) were associated with lower usage. It is unclear how effective the LifeStraw is, given low rates of compliance and the possibility of reporting bias. Of the measures reported this year to purify water, slow sand filtration seemed the most promising. In recent years RCTs of ceramic filtration has also been successful in reducing diarrhoeal morbidity in several African countries.

Trop Med Int Health. 2009 Nov;14(11):1374-82. Epub 2009 Sep 4.

<http://www3.interscience.wiley.com/cgi-bin/fulltext/122589724/PDFSTART>

Intermittent slow sand filtration for preventing diarrhoea among children in Kenyan households using unimproved water sources: randomized controlled trial.

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Abstract

OBJECTIVE: Measure effectiveness of intermittent slow sand filtration for reducing child diarrhoea among households using unimproved water sources in rural Kenya. **METHODS:** A randomized controlled trial was conducted among populations meeting a high-risk profile for child diarrhoea from drinking river water in the River Njoro watershed. **Intervention households (30) were provided the concrete BioSand Filter and instructed on filter use and maintenance. Control households (29) continued normal practices. Longitudinal monthly monitoring of diarrhoea (seven-day daily prevalence recall) and of influent, effluent, and**

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drinking water quality for fecal coliform was conducted for 6 months. RESULTS: Intervention households had better drinking water quality than control households (fecal coliform geometric mean, 30.0 CFU vs. 89.0 CFU/100 ml, $P < 0.001$) and reported significantly fewer diarrhoea days (86 days over 626 child-weeks) compared to controls (203 days over 558 child-weeks) among children up to 15 (age-adjusted RR 0.46; 95 % CI = 0.22, 0.96). Greater child diarrhoea reduction due to the intervention (age-adjusted RR 0.23, 95 % CI = 0.10, 0.51) was observed among the sub-group using unimproved water sources all of the time. **CONCLUSION:** Intermittent slow sand filtration, a non-commercial technology, produces similar observed effects on child diarrhoea as commercial POU products, adding to the range of effective options for poor populations (chlorination, ceramic filtration, solar disinfection, flocculation/disinfection).

Am J Trop Med Hyg. 2010 Jan;82(1):16-22.

Sodium dichloroisocyanurate tablets for routine treatment of household drinking water in periurban Ghana: a randomized controlled trial.

Jain S, Sahanoon OK, Blanton E, Schmitz A, Wannemuehler KA, Hoekstra RM, Quick RE.

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Abstract

We conducted a randomized, placebo-controlled, triple-blinded trial to determine the health impact of daily use of sodium dichloroisocyanurate (NaDCC) tablets for household drinking water treatment in periurban Ghana. We randomized 240 households (3,240 individuals) to receive either NaDCC or placebo tablets. All households received a 20-liter safe water storage vessel. Over 12 weeks, 446 diarrhea episodes (2.2%) occurred in intervention and 404 (2.0%) in control households ($P = 0.38$). Residual free chlorine levels indicated appropriate tablet use. **Escherichia coli was found in stored water at baseline in 96% of intervention and 88% of control households and at final evaluation in 8% of intervention and 54% of control households ($P = 0.002$).** NaDCC use did not prevent diarrhea but improved water quality. Diarrhea rates were low and water quality improved in both groups. Safe water storage vessels may have been protective. A follow-up health impact study of NaDCC tablets is warranted.

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PLoS Med. 2009 Aug;6(8):e1000125. Epub 2009 Aug 18.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000125>

Solar drinking water disinfection (SODIS) to reduce childhood diarrhoea in rural Bolivia: a cluster-randomized, controlled trial.

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Abstract

BACKGROUND: Solar drinking water disinfection (SODIS) is a low-cost, point-of-use water purification method that has been disseminated globally. Laboratory studies suggest that SODIS is highly efficacious in inactivating waterborne pathogens. Previous field studies provided limited evidence for its effectiveness in reducing diarrhoea. **METHODS AND FINDINGS:** We conducted a **cluster-randomized controlled trial in 22 rural communities in Bolivia to evaluate the effect of SODIS in reducing diarrhoea among children under the age of 5 y.** A local nongovernmental organisation conducted a standardised interactive SODIS-promotion campaign in 11 communities targeting households, communities, and primary schools. Mothers completed a daily child health diary for 1 y. Within the intervention arm 225 households (376 children) were trained to expose water-filled polyethyleneteraphtalate bottles to sunlight. Eleven communities (200 households, 349 children) served as a control. We recorded 166,971 person-days of observation during the trial representing 79.9% and 78.9% of the total possible person-days of child observation in intervention and control arms, respectively. Mean compliance with SODIS was 32.1%. **The reported incidence rate of gastrointestinal illness in children in the intervention arm was 3.6 compared to 4.3 episodes/year at risk in the control arm. The relative rate of diarrhoea adjusted for intracluster correlation was 0.81 (95% confidence interval 0.59-1.12).** The median length of diarrhoea was 3 d in both groups. **CONCLUSIONS: Despite an extensive SODIS promotion campaign we found only moderate compliance with the intervention and no strong evidence for a substantive reduction in diarrhoea among children.** These results suggest that there is a need for better evidence of how the well-established laboratory efficacy of this home-based water treatment method translates into field effectiveness under various cultural settings and intervention intensities. Further global promotion of SODIS for general use should be undertaken with care until such evidence is available.

Environ Sci Technol. 2009 Aug 1;43(15):5934-9.

Randomized controlled trial in rural Ethiopia to assess a portable water treatment device.

Boisson S, Schmidt WP, Berhanu T, Gezahegn H, Clasen T.

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Abstract

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We conducted a randomized controlled trial to assess the Lifestraw Personal pipe-style water treatment device among a rural population in Ethiopia. A total of 313 households (including 1516 persons) were randomly assigned either to an intervention group in which each householder received a Lifestraw Personal or a control. Households were visited fortnightly over a five-month intervention period and asked to report any episode of diarrhea during the previous week. A random sample of 160 devices was tested each month to assess the presence of thermotolerant coliforms (TTC) and residual iodine in treated water and to measure flow rate under simulated use. **Members of the intervention group had 25% fewer weeks with diarrhea than those of the control group (longitudinal prevalence ratio = 0.75; 95% CI 0.60; 0.95).** All 718 filtered water samples were free of TTC, were free of detectable iodine disinfectant, and showed a constant flow rate over time. After the five-month intervention period, 34% of participants reported use of device in the preceding week and 13% reported consistent use. **While the device was associated with a 25% reduction in longitudinal prevalence of diarrhea, low levels of use suggest that much of this effect is likely to be attributable to reporting bias that is common in open trials with nonobjective outcomes.**

Comment

The "LifeStraw Personal" is a drinking straw made of plastic, resembling a flute, about 30 cm long and 30 mm in diameter. Inside are filters and a chamber impregnated with iodine. These remove the bacteria from the water as it is drunk. Water that is sucked through the straw passes through a filter of 100-micrometer pores, then through a mesh of 15-micrometer pores. Water then passes through a chamber with iodine-coated beads. The water then finally passes through carbon, designed to remove the iodide taste and medium-sized bacteria. The movement of water is by suction, as when using an ordinary drinking straw. The cost is around \$3.50 per straw, and the straw is said to filter 700 litres of water. <http://news.bbc.co.uk/2/hi/africa/4967452.stm>

Ear, nose and throat problems

Int J Pediatr Otorhinolaryngol. 2009 Dec;73(12):1696-701. Epub 2009 Sep 27.

Efficacy of nasal irrigation in the treatment of acute sinusitis in children.

Wang YH, Yang CP, Ku MS, Sun HL, Lue KH.

Division of Allergy, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan.

Abstract

BACKGROUND: Nasal irrigation has been used as an adjunctive therapy of sinonasal disease including acute/chronic sinusitis and allergic rhinitis. Several published articles reported it also improves clinical sinus symptoms. **OBJECTIVE:** To evaluate the effectiveness of normal saline nasal irrigation in the management of acute sinusitis in children. **DESIGN:** This was a randomized, prospective placebo-controlled study. **METHODS:** We included 69 participants with acute sinusitis. 30 of 69 participants underwent normal saline nasal irrigation. 39 of 69 participants were not receiving nasal irrigation. All participants performed nasal peak expiratory flow rate (nPEFR) test, nasal smear examination, radiography (Water's projection) and requested to complete the Pediatric Rhinoconjunctivitis Quality of Life Questionnaires

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(PRQLQ) at the baseline visit. All participants were requested to record the symptom diary card every day and were followed-up every 1 week during this period. A physical examination, nasal smear and nPEFR were performed at each visit, and all daily diary cards collected. At the final visit, the symptoms diaries were reviewed and participants were requested to complete the PRQLQ again. The nPEFR, radiography (Water's projection) and nasal smear were also repeated. RESULTS: Normal saline irrigation group significantly improved mean PRQLQ values and nPEFR values at medium (T=2.816, P<0.05) and final period (T=2.767, P<0.05) compared with the other group. Although there were no statically significant improving rate of radiography (Water's projection) in among two groups (T=0.545, P>0.05), but normal saline irrigation group was better than the other group. The improval rate of mean TSS in the irrigation group significantly improved all symptoms compared with the placebo group, in which rhinorrhea, nasal congestion, throat itching, cough and sleep quality improved. 27 of 66 (40.9%) participants with atopy, 16 of 27 (53.33%) participants underwent normal saline irrigation. Normal saline irrigation atopy group significantly improved rhinorrhea, nasal congestion, throat itching and sleep quality symptoms compared with non-irrigation atopy group. Normal saline irrigation atopy group significantly improved nPEFR values at final period (Z=2.53, P<0.05). CONCLUSION: This study evidence that normal saline nasal irrigation improves Pediatric Rhinoconjunctivitis Quality of Life and decreases acute sinusitis symptoms. Nasal irrigation is an effective adjunctive treatment for pediatric acute sinusitis. Normal saline nasal irrigation in atopy children also improves allergic-related symptoms. We may need larger, longer and extended study to assess the conclusion.

Emergency care

Crit Care Med. 2010 Jun 3. [Epub ahead of print]

Phase II trial on the use of Dextran 70 or starch for supportive therapy in Kenyan children with severe malaria.

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Abstract

OBJECTIVES:: A previous meta-analysis has shown a consistent survival benefit in children with severe malaria receiving human albumin solution compared to other resuscitation fluids. **Human albumin solution is expensive and not readily available in Africa.** We examined the **safety and efficacy of the fluid resuscitation with two synthetic colloids, Dextran 70 and hydroxyethyl starch**, to inform future trial design. DESIGN:: An open-label randomized, controlled, phase II safety and efficacy trial. SETTING:: High-dependency unit, Kilifi District Hospital, Kenya. PATIENTS: **Children aged >6 months with severe falciparum malaria and acidosis (base deficit >8 mmol).** INTERVENTIONS:: Boluses (20-40 mL/kg) of 6% Dextran 70 and 6% hydroxyethyl starch (130/0.4). MEASUREMENTS AND MAIN RESULTS::

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Primary end point: resolution of shock over 8 hrs. Secondary end points include resolution of acidosis, in-hospital mortality, and adverse events (allergic reactions, pulmonary edema, and neurologic sequelae). A total of 79 children were enrolled: 39 received Dextran 70 and 40 received hydroxyethyl starch. **No significant difference was observed in Dextran 70 and hydroxyethyl starch groups for shock resolution at 8 hrs: 23/37 (62%) and 25/39 (64%), respectively (p = .99).** Acidosis resolution and respiratory distress were marginally superior in the hydroxyethyl starch group: 3/39 (8%) remained acidotic at 8 hrs versus 10/37 (27%) in the Dextran 70 arm (p = .05). There were four deaths (5%): two per arm, including three deaths in the coma subgroup (3/39, 8%). No other new adverse event was reported. **CONCLUSIONS:: Correction of shock by volume expansion with either Dextran 70 or hydroxyethyl starch in children with severe malaria acidosis is safe with low mortality, including the highest risk cases admitted in coma.** Both solutions present an attractive and practical option for consideration in future volume resuscitation trials in severe malaria.

Ethics

Bull World Health Organ. 2009 Oct;87(10):772-9.

<http://www.scielosp.org/pdf/bwho/v87n10/a13v8710.pdf>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2755306/?tool=pubmed>

Ethical challenges in cluster randomized controlled trials: experiences from public health interventions in Africa and Asia.

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Abstract

Public health interventions usually operate at the level of groups rather than individuals, and cluster randomized controlled trials (RCTs) are one means of evaluating their effectiveness. Using examples from six such trials in Bangladesh, India, Malawi and Nepal, we discuss our experience of the ethical issues that arise in their conduct. We set cluster RCTs in the broader context of public health research, highlighting debates about the need to reconcile individual autonomy with the common good and about the ethics of public health research in low-income settings in general. After a brief introduction to cluster RCTs, we discuss particular challenges we have faced. These include the nature of - and responsibility for - group consent, and the need for consent by individuals within groups to intervention and data collection. We discuss the timing of consent in relation to the implementation of public health strategies, and the problem of securing ethical review and approval in a complex domain. Finally, we consider the debate about benefits to control groups and the standard of care that they should receive, and the issue of post-trial adoption of the intervention under test.

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BMC Med Ethics. 2010 May 14;11:8.

<http://www.biomedcentral.com/1472-6939/11/8>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2877053/?tool=pubmed>

Comparison of group counseling with individual counseling in the comprehension of informed consent: a randomized controlled trial.

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Abstract

BACKGROUND: Studies on different methods to supplement the traditional informed consent process have generated conflicting results. This study was designed to evaluate whether participants who received group counseling prior to administration of informed consent understood the key components of the study and the consent better than those who received individual counseling, based on the hypothesis that group counseling would foster discussion among potential participants and enhance their understanding of the informed consent.

METHODS: Parents of children participating in a trial of nutritional supplementation were randomized to receive either group counseling or individual counseling prior to administration of the informed consent. To assess the participant's comprehension, a structured questionnaire was administered approximately 48-72 hours afterwards by interviewers who were blinded to the allocation group of the respondents. **RESULTS:** A total of 128 parents were recruited and follow up was established with 118 (90.2%) for the study. All respondents were aware of their child's participation in a research study and the details of sample collection. However, their understanding of study purpose, randomization and withdrawal was poor. There was no difference in comprehension of key elements of the informed consent between the intervention and control arm. **CONCLUSIONS:** The results suggest that the group counseling might not influence the overall comprehension of the informed consent process. Further research is required to devise better ways of improving participants' understanding of randomization in clinical trials.

HIV / AIDS

(see also Development)

Anti-retroviral therapy

Antivir Ther. 2010;15(1):83-90.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2867092/?tool=pubmed>

Pharmacokinetics of generic and trade formulations of lamivudine, stavudine and nevirapine in HIV-infected Malawian children.

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Corbett AH, Hosseinipour MC, Nyirenda J, Kanyama C, Rezk NL, Mkupani P, Sichali D, Tien H, Kashuba AD, Mwansambo C, Weigel R, Kazembe P.

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Abstract

BACKGROUND: The aim of this study was to evaluate the pharmacokinetics of lamivudine (3TC), stavudine (d4T) and nevirapine (NVP) in HIV-infected Malawian children receiving quartered tablet multiples of Triomune 40 (generic tablet [GT]) compared with individual generic liquid (GL) and trade liquid (TL). **METHODS:** This was a prospective randomized three-way crossover study. Patients (8-<12 kg, 18-<22 kg or 28-<32 kg body weight) taking Triomune 40 were recruited and randomized to receive GT twice daily (one-quarter, one-half or three-quarter tablets using Malawi treatment guidelines), GL twice daily (in the equivalent dose of GT) or TL twice daily (dosed using weight and age from US Department of Health and Human Services paediatric treatment guidelines). After 10 days of one formulation, 6-h pharmacokinetic sampling was performed, and patients were crossed over to subsequent formulations. Baseline concentration (C(0 h)), area under the curve (AUC)(0-6 h), maximum plasma concentration (C(max)) and time to C(max) were generated for each antiretroviral treatment. **RESULTS:** A total of 7 males and 11 females (6 in each GT dosing group) with a median (range) age of 7.2 years (1.3-13.6), weight of 19 kg (9.0-30.5) and height of 109 cm (75-132) were recruited. Combining all patients, no difference in pharmacokinetics was noted among the formulations for all drugs. However, patients in the one-quarter GT dosing group (8-<12 kg) had lower 3TC exposures than with the GL or TL (3TC AUC(0-6 h) 1,102, 1,720 and 2,060 h*ng/ml, respectively; P<0.005) and had more subtherapeutic NVP C(0 h) (10 of 13 occasions versus the one-half and three-quarter tablet groups). Compared with Western paediatric cohorts, Malawians had concentrations 30-40% lower for 3TC and d4T and 50% higher for NVP. **CONCLUSIONS:** Quartered multiples of Triomune 40 are appropriate for children 18-<22 kg and 28-<32 kg in weight; however, alternative formulations are suggested in children weighing 8-<12 kg.

Comment

*Triomune is a generic antiretroviral combination tablet therapy, the cost of which is less than 10% the cost of trade liquid products. Use of cheaper generic tablets has enabled the scale up of ART in many low income countries. Whether such fixed-dose combination (FDC) tablets can be halved or quartered and still provide doses that are safe and effective is important. This study found that the generic FDC tablets were appropriate for older children, but for young children and infants generic smaller **whole** FDC tablets (such as Triomune Junior and Triomune Baby) will be more appropriate.*

Management of HIV-related conditions

J Nutr. 2010 May;140(5):969-74. Epub 2010 Mar 24.

Short-term micronutrient supplementation reduces the duration of pneumonia and diarrheal episodes in HIV-infected children.

Mda S, van Raaij JM, de Villiers FP, MacIntyre UE, Kok FJ.

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Abstract

The duration of pneumonia and of diarrhea is reported to be longer in HIV-infected than in uninfected children. We assessed the effect of a multi-micronutrient supplement on the duration of hospitalization in HIV-infected children. **In a double-blind, randomized trial, HIV-infected children (4-24 mo) who were hospitalized with diarrhea or pneumonia were enrolled (n = 118) and given a daily dose of a multi-micronutrient supplement (containing vitamins A, B complex, C, D, E, and folic acid, as well as copper, iron, and zinc at levels based on recommended daily allowances) or a placebo until discharge from the hospital.** Children's weights and heights were measured after enrollment and micronutrient concentrations were measured before discharge. On recovery from diarrhea or pneumonia, the children were discharged and the duration of hospitalization was noted. Anthropometric indices and micronutrient concentrations did not differ between children who received supplements and those who received placebos. Overall, the duration of hospitalization was shorter ($P < 0.05$) among children who were receiving supplements (7.3 +/- 3.9 d) (mean +/- SD) than in children who were receiving placebos (9.0 +/- 4.9); this was independent of admission diagnosis. In children admitted with diarrhea, the duration of hospitalization was 1.6 d (19%) shorter among children receiving supplements than in those receiving placebos, and hospitalization for pneumonia was 1.9 d (20%) shorter among children receiving supplements. **Short-term multi-micronutrient supplementation significantly reduced the duration of pneumonia or diarrhea in HIV-infected children who were not yet receiving antiretroviral therapy and who remained alive during hospitalization.**

BMC Infect Dis. 2009 Dec 2;9:195.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2794874/?tool=pubmed>

<http://www.biomedcentral.com/1471-2334/9/195>

High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial.

Amadi B, Mwiya M, Sianongo S, Payne L, Watuka A, Katubulushi M, Kelly P.

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Abstract

BACKGROUND: Treatment of cryptosporidiosis in HIV infected children has proved difficult and unsatisfactory with no drugs having demonstrable efficacy in controlled trials except nitazoxanide. We hypothesised that a prolonged course of treatment with high dose nitazoxanide would be effective in treating cryptosporidiosis in HIV positive Zambian children. **METHODS:** We performed a double-blind, randomised, placebo controlled trial in paediatric patients in the UTH in Lusaka. The study included HIV positive children between one and eleven years of age

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if 2 out of 3 stool samples were positive for oocysts of *Cryptosporidium* spp. Children were given nitazoxanide suspension in a dose of 200 mg twice daily (bid) for 28 days (if 1-3 years old) or 400 mg bid for 28 days (if 4-11 years old), or matching placebo. RESULTS: Sixty children were randomised and 52 were fully evaluated. Only five children were 4 years of age or over and received the higher dose. **In the primary efficacy analysis, 11 out of 26 (42%) in the active treatment group achieved a 'Well' clinical response compared to 8 out of 26 (35%) in the placebo group. Parasitological response was declared as 'Eradicated' in 27% in the active group and 35% in the placebo group.** Mortality (16/52, 31%) did not differ by treatment allocation. CONCLUSION: We found no significant benefit in children with cryptosporidiosis despite high dose and longer treatment duration. This is the second randomised controlled trial to suggest that in Zambian children with HIV-related immunosuppression nitazoxanide does not eradicate this infection nor provide clinical symptom reduction.

Prevention of parent to child transmission

PLoS Med. 2009 Oct;6(10):e1000172. Epub 2009 Oct 27.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000172>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2760761/?tool=pubmed>

Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial.

McIntyre JA, Hopley M, Moodley D, Eklund M, Gray GE, Hall DB, Robinson P, Mayers D, Martinson NA.

Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa.

Abstract

BACKGROUND: Single-dose nevirapine (sdNVP)-which prevents mother-to-child transmission of HIV-selects non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance mutations in the majority of women and HIV-infected infants receiving it. This open-label, randomised trial examined the **efficacy of short-course zidovudine (AZT) and lamivudine (3TC) with sdNVP in reducing NNRTI resistance in mothers, and as a secondary objective, in infants, in a setting where sdNVP was standard-of-care.** **METHODS AND FINDINGS:** sdNVP alone, administered at the onset of labour and to the infant, was compared to sdNVP with AZT plus 3TC, given as combivir (CBV) for 4 (NVP/CBV4) or 7 (NVP/CBV7) days, initiated simultaneously with sdNVP in labour; their newborns received the same regimens. Women were randomised 1ratio1ratio1. HIV-1 resistance was assessed by population sequencing at: baseline, 2, and 6 wk after birth. An unplanned interim analysis resulted in early stopping of the sdNVP arm. 406 pregnant women were randomised and took study medication (sdNVP 74, NVP/CBV4 164, and NVP/CBV7 168). **HIV-1 resistance mutations emerged in 59.2%, 11.7%, and 7.3% of women in the sdNVP, NVP/CBV4, and NVP/CBV7 arms by 6**

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wk postpartum; differences between NVP-only and both NVP/CBV arms were significant ($p < 0.0001$), but the difference between NVP/CBV4 and NVP/CBV7 was not ($p = 0.27$). Estimated efficacy comparing combined CBV arms with sdNVP was 85.6%. Similar resistance reductions were seen in infants who were HIV-infected by their 6-wk visit. **CONCLUSIONS:** A short course of AZT plus 3TC, supplementing maternal and infant sdNVP, reduces emergent NNRTI resistance mutations in both mothers and their infants. However, this trial was not powered to detect small differences between the CBV arms.

J Antimicrob Chemother. 2009 Dec;64(6):1265-73. Epub 2009 Oct 6.

<http://jac.oxfordjournals.org/cgi/reprint/64/6/1265>

Influence of CYP2B6 polymorphisms on the persistence of plasma nevirapine concentrations following a single intra-partum dose for the prevention of mother to child transmission in HIV-infected Thai women.

Chantarangsu S, Cressey TR, Mahasirimongkol S, Capparelli E, Tawon Y, Ngo-Giang-Huong N, Jourdain G, Lallemant M, Chantratita W.

Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Abstract

OBJECTIVES: To investigate the association of single nucleotide polymorphisms (SNPs) with nevirapine concentrations following intra-partum single-dose nevirapine. **METHODS:** Plasma and DNA samples were obtained from 330 HIV-infected Thai women who received intra-partum single-dose nevirapine in the PHPT-2 clinical trial to prevent perinatal HIV transmission. Nine SNPs within CYP2B6, CYP3A4 and ABCB1 were genotyped by real-time PCR. Nevirapine plasma concentrations were determined by HPLC and used in a population pharmacokinetic analysis. **RESULTS:** Higher nevirapine exposure was observed in women carrying the CYP2B6 516G>T polymorphism, but this did not reach statistical significance ($P = 0.054$). The TGATC CYP2B6 haplotype (g.3003T, 516G, 785A, g.18492T and g.21563C) was associated with increased nevirapine clearance and lower exposure ($P = 0.0029$). The median time for nevirapine concentrations to reach 10 ng/mL post-partum (nevirapine IC(50) for HIV-1) was 14 days [interquartile range (IQR, 14-18)] for TGATC homozygotes, 16 days (14-20) for TGATC heterozygotes and 18 days (14-20) for non-TGATC homozygotes ($P = 0.020$). **CONCLUSIONS:** The CYP2B6 516G>T impact on nevirapine concentrations was less pronounced after intra-partum single-dose nevirapine than reported under steady-state conditions, perhaps due to lack of enzyme auto-induction at the time of dosing. Although the TGATC CYP2B6 haplotype may shorten the persistence of nevirapine post-partum, its practical implications for the prevention of HIV transmission or selection of resistance mutations are likely limited.

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J Acquir Immune Defic Syndr. 2009 Oct 1;52(2):273-9.

Predictors of rapid HIV testing acceptance and successful nevirapine administration in Zambian labor wards.

Megazzini KM, Chintu N, Vermund SH, Redden DT, Krebs DW, Simwenda M, Tambatamba B, Sinkala M, Stringer JS.

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Abstract

BACKGROUND: Provision of HIV testing in labor provides an opportunity to reach susceptible women and infants. **METHODS:** As part of a cluster randomized trial of labor ward-based prevention of mother-to-child transmission services in Lusaka, Zambia, we determined predictors of testing acceptance and nevirapine (NVP) administration in labor. HIV counseling and testing were offered to women unaware of their HIV status. NVP was administered to women who tested positive, and an inert (calcium) tablet was provided to women who tested negative, to avoid stigmatization. **RESULTS:** Among the 2435 women who presented in labor, 393 (16%) were unaware of their HIV status, of whom 278 (71%) met eligibility criteria. **We offered counseling to 217 (78%) of eligible women: 146 (67%) agreed, 82 (56%) of those counseled were tested for HIV, and 23 (28%) were seropositive.** Testing rates were higher among primigravida women [adjusted odds ratio (AOR) 1.5; 95% confidence interval (CI): 1.1 to 2.1] and among those not offered HIV testing during their pregnancy (AOR 3.7; 95% CI: 2.8 to 5.1). Cervical dilation ≤ 3 cm at the time of admission was associated strongly with NVP ingestion >1 hour (AOR 11.5; 95% CI: 4.5 to 29.2) and >2 hours (AOR 11.4; 95% CI: 4.7 to 27.5) before delivery. **CONCLUSION: Labor ward HIV testing is feasible in this resource-limited setting.**

J Acquir Immune Defic Syndr. 2009 Sep 1;52(1):32-9.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767188/?tool=pubmed>

Predictors of early and late mother-to-child transmission of HIV in a breastfeeding population: HIV Network for Prevention Trials 012 experience, Kampala, Uganda.

Mmiro FA, Aizire J, Mwatha AK, Eshleman SH, Donnell D, Fowler MG, Nakabiito C, Musoke PM, Jackson JB, Guay LA.

Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda.

Abstract

OBJECTIVE: To determine the predictors for early versus later (breastfeeding) transmission of HIV-1. **METHODS:** Secondary data analysis was performed on HIV Network for Prevention Trials 012, a completed randomized clinical trial assessing the relative efficacy of nevirapine (NVP) versus zidovudine in reducing mother-to-child transmission (MTCT) of HIV-1. We used Cox regression analysis to assess risk factors for MTCT. The ViroSeq HIV genotyping and a sensitive point mutation assay were used to detect NVP resistance mutations. **RESULTS:** In this subset analyses, **122 of 610 infants were HIV infected, of whom 99 (81.1%) were infected**

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early (first positive polymerase chain reaction < or =56 days). Incidence of MTCT after 56 days was low [0.7% per month (95% confidence interval, CI: 0.4 to 1.0)], but continued through 18 months. In multivariate analyses, early MTCT "factors" included NVP versus zidovudine (hazard ratio (HR) = 0.57, 95% CI: 0.38 to 0.86), pre-entry maternal viral load (VL, HR = 1.76, 95% CI: 1.28 to 2.41), and CD4 cell count (HR = 1.16, 95% CI: 1.05 to 1.28). Maternal VL (6-8 weeks) was associated with late MTCT (HR = 3.66, 95% CI: 1.78 to 7.50), whereas maternal NVP resistance (6-8 weeks) was not. **CONCLUSIONS:** Maternal VL was the best predictor of both early and late transmission. Maternal NVP resistance at 6-8 weeks did not predict late transmission.

BMC Pediatr. 2009 Aug 7;9:49.

<http://www.biomedcentral.com/1471-2431/9/49>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746190/?tool=pubmed>

Selected hematologic and biochemical measurements in African HIV-infected and uninfected pregnant women and their infants: the HIV Prevention Trials Network 024 protocol.

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Abstract

BACKGROUND: Reference values for hematological and biochemical assays in pregnant women and in newborn infants are based primarily on Caucasian populations. Normative data are limited for populations in sub-Saharan Africa, especially comparing women with and without HIV infection, and comparing infants with and without HIV infection or HIV exposure. **METHODS:** We determined HIV status and selected hematological and biochemical measurements in women at 20-24 weeks and at 36 weeks gestation, and in infants at birth and 4-6 weeks of age. All were recruited within a randomized clinical trial of antibiotics to prevent chorioamnionitis-associated mother-to-child transmission of HIV (HPTN024). We report nearly complete laboratory data on 2,292 HIV-infected and 367 HIV-uninfected pregnant African women who were representative of the public clinics from which the women were recruited. Nearly all the HIV-infected mothers received nevirapine prophylaxis at the time of labor, as did their infants after birth (always within 72 hours of birth, but typically within just a few hours at the four study sites in Malawi (2 sites), Tanzania, and Zambia). **RESULTS:** HIV-infected pregnant women had lower red blood cell counts, hemoglobin, hematocrit, and white blood cell counts than HIV-uninfected women. Platelet and monocyte counts were higher among HIV-infected women at both time points. At the 4-6-week visit, HIV-infected infants had lower hemoglobin, hematocrit and white blood cell counts than uninfected infants. Platelet counts were lower in HIV-infected infants than HIV-uninfected infants, both at birth and at 4-6 weeks of age. At 4-6 weeks, HIV-infected infants had higher alanine aminotransferase measures than uninfected infants. **CONCLUSION:** Normative data in pregnant African women and their newborn infants are needed to guide the large-scale HIV care and treatment programs being

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scaled up throughout the continent. These laboratory measures will help interpret clinical data and assist in patient monitoring in a sub-Saharan Africa context.

Haematology

Eur J Haematol. 2010 Jan 1;84(1):52-8. Epub 2009 Oct 3.

Effect of combination therapy of hydroxyurea with l-carnitine and magnesium chloride on hematologic parameters and cardiac function of patients with beta-thalassemia intermedia.

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Abstract

BACKGROUND: l-Carnitine and magnesium have antioxidant properties. They have the potential to stimulate production of fetal hemoglobin and stabilize the RBC membrane, respectively. Several studies have also shown the beneficial effects of hydroxyurea in thalassemic patients. We assessed the effect of combination therapy of hydroxyurea with l-carnitine and magnesium chloride on hematologic parameters and cardiac function of patients with beta-thalassemia intermedia. **METHODS:** One-hundred-and-twenty patients with thalassemia intermedia (range, 4-35 yr; mean, 19 +/- 6.4 yr) who had no need for blood transfusion or requirement for blood transfusion with an interval of >6 months were randomly selected. All patients had been on hydroxyurea for >6 months. They were randomly divided into four groups: group A (hydroxyurea alone); group B (hydroxyurea and l-carnitine); group C (hydroxyurea and magnesium chloride); and group D (hydroxyurea, l-carnitine and magnesium chloride). **RESULTS:** In groups B, C, and D, mean Hb and hematocrit increased during 6-month treatment ($P < 0.001$). Echocardiographic studies revealed a significant decrease in left ventricular end-diastolic diameter in group B ($P = 0.032$), increase in pulmonary acceleration time in group C ($P = 0.012$), and increase in left ventricular ejection fraction in groups C and D ($P < 0.000$ and 0.006 , respectively). **CONCLUSION:** Combination of hydroxyurea with l-carnitine or magnesium could be more effective in improving hematologic parameters and cardiac status in patients with beta-thalassemia intermedia than hydroxyurea alone.

Helminth and other gastrointestinal infections

(See also Anaemia, Diarrhoea)

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Clin Exp Allergy. 2010 Jan;40(1):131-42. Epub 2009 Sep 15.

Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam.

Flohr C, Tuyen LN, Quinnell RJ, Lewis S, Minh TT, Campbell J, Simmons C, Telford G, Brown A, Hien TT, Farrar J, Williams H, Pritchard DI, Britton J.

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Abstract

BACKGROUND: Observational evidence suggests that infection with helminths protects against allergic disease and allergen skin sensitization. It is postulated that such effects are mediated by helminth-induced cytokine responses, in particular IL-10. **OBJECTIVE:** We tested this hypothesis in a rural area of central Vietnam where hookworm infection is endemic. **METHODS: One thousand five hundred and sixty-six schoolchildren aged 6-17 were randomly allocated to receive either anti-helminthic therapy or a placebo at 0, 3, 6, and 9 months.** We compared changes in the prevalence of exercise-induced bronchoconstriction, allergen skin sensitization, flexural eczema on skin examination, questionnaire-reported allergic disease (wheeze and rhinitis symptoms), and immunological parameters (hookworm-induced IFN-gamma, IL-5, IL-10) between 0 and 12 months. **RESULTS:** One thousand four hundred and eighty-seven children (95% of these randomized) completed the study. The most common helminth infections were hookworm (65%) and *Ascaris lumbricoides* (7%). **There was no effect of the therapy on the primary outcome,** exercise-induced bronchoconstriction (within-participant mean percent fall in peak flow from baseline after anti-helminthic treatment 2.25 (SD 7.3) vs. placebo 2.19 (SD 7.8, P=0.9), or on the prevalence of questionnaire-reported wheeze [adjusted odds ratio (OR)=1.16, 95% confidence interval (CI) 0.35-3.82, P=0.8] and rhinitis (adjusted OR=1.39, 0.89-2.15, P=0.1), or flexural dermatitis on skin examination (adjusted OR=1.15, 0.39-3.45, P=0.8). However, anti-helminthic therapy was associated with a significantly higher allergen skin sensitization risk (adjusted OR=1.31, 1.02-1.67, P=0.03). This effect was particularly strong for children infected with *A. lumbricoides* at baseline (adjusted OR=4.90, 1.48-16.19, P=0.009). Allergen skin sensitization was inversely related to hookworm-specific IL-10 at baseline (adjusted OR=0.76, 0.59-0.99, P=0.04). No cytokine tested, including IL-10, changed significantly after the anti-helminthic therapy compared with the placebo. **CONCLUSION: A significant reduction in worm burden over a 12-month period in helminth-infected children increases the risk of allergen skin sensitization but not of clinical allergic disease.** The effect on skin sensitization could not be fully explained by any of the immunological parameters tested.

Helicobacter. 2009 Jun;14(3):202-7.

<http://www3.interscience.wiley.com/cgi-bin/fulltext/122381560/PDFSTART>

Long-term administration of probiotics to asymptomatic pre-school children for either the eradication or the prevention of *Helicobacter pylori* infection.

Boonyaritichai S, Kuwabara K, Nagano J, Kobayashi K, Koga Y.

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Abstract

BACKGROUND: The role of probiotics in the armamentarium remains to be defined. The aims of this study were to investigate whether the long-time administration of *Lactobacillus gasseri* OLL2716 (LG21) strain can eradicate *H. pylori* in asymptomatic pre-school children and/or prevent *H. pylori* infection. **METHODS:** **A total of 440 children, from 5-7 years of age, attending a kindergarten in Thailand** were screened by the *Helicobacter pylori* stool antigen (HpSA) test. Thereafter 132 *H. pylori* positive and 308 *H. pylori* negative children were recruited to eradication and randomized prevention arms, respectively. **Children in the active and placebo treatment groups received *Lactobacillus gasseri* OLL2716 (LG21) containing cheese and ordinary cheese, respectively, for 12 months.** Eradication was defined as reversion by HpSA at 12 months. Prevention was defined as persistently HpSA negative at 12 months. **RESULTS:** Eighty-two of 132 *H. pylori* positive (62%) completed the eradication arm, of which 24 (29.3%) were negative at 12 months according to the HpSA test. **In the randomized prevention arm, 123 of 156 (79%) and 99 of 122 (81%) completed active and placebo arms, respectively, of which 4.1% and 8.1%, respectively, were HpSA positive at 12 months based on a per-protocol analysis (p = .21).** **CONCLUSION:** Further trials are needed.

Hygiene

Trop Med Int Health. 2009 Oct;14(10):1303-14. Epub 2009 Aug 25.

<http://www3.interscience.wiley.com/cgi-bin/fulltext/122577129/PDFSTART>

The effect of a soap promotion and hygiene education campaign on handwashing behaviour in rural India: a cluster randomised trial.

Biran A, Schmidt WP, Wright R, Jones T, Seshadri M, Isaac P, Nathan NA, Hall P, McKenna J, Granger S, Bidinger P, Curtis V.

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Abstract

OBJECTIVE: To investigate the **effectiveness of a hygiene promotion intervention based on germ awareness in increasing handwashing with soap** on key occasions (after faecal contact and before eating) in rural Indian households. **METHODS:** Cluster randomised trial of a hygiene promotion intervention in five intervention and five control villages. Handwashing was assessed through structured observation in a random sample of 30 households per village. Additionally, soap use was monitored in a sub-sample of 10 households per village using electronic motion detectors embedded in soap bars. **RESULTS:** The intervention reached 40% of the target population. Germ awareness increased as well as reported handwashing (a possible indicator of

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perceived social norms). **Observed handwashing with soap on key occasions was rare (6%), especially after faecal contact (2%). Observed handwashing with soap on key occasions did not change 4 weeks after the intervention in either the intervention arm (-1%, 95% CI -2%/+0.3%), or the control arm (+0.4%, 95% CI -1%/+2%).** Data from motion detectors indicated a significant but small increase in overall soap use in the intervention arm. We cannot confidently identify the nature of this increase except to say that there was no change in a key measure of handwashing after defecation. **CONCLUSION:** The intervention proved scalable and effective in raising hygiene awareness. There was some evidence of an impact on soap use but not on the primary outcome of handwashing at key times. However, the results do not exclude that changes in knowledge and social norms may lay the foundations for behaviour change in the longer term.

Bull World Health Organ. 2009 Aug;87(8):580-7.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2733281/?tool=pubmed>

<http://www.scielo.org/pdf/bwho/v87n8/v87n8a13.pdf>

Shame or subsidy revisited: social mobilization for sanitation in Orissa, India.

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Abstract

OBJECTIVE: To determine the effectiveness of a sanitation campaign that combines 'shaming' (i.e. emotional motivators) with subsidies for poor households in rural Orissa, an Indian state with a disproportionately high share of India's child mortality. **METHODS:** Using a cluster-randomized design, we selected 20 treatment and 20 control villages in the coastal district of Bhadrak, rural Orissa, for a total sample of 1050 households. We collected sanitation and health data before and after a community-led sanitation project, and we used a difference-in-difference estimator to determine the extent to which the campaign influenced the number of households building and using a latrine. **FINDINGS: Latrine ownership did not increase in control villages, but in treatment villages it rose from 6% to 32% in the overall sample, from 5% to 36% in households below the poverty line (eligible for a government subsidy) and from 7% to 26% in households above the poverty line (not eligible for a government subsidy).** **CONCLUSION:** Subsidies can overcome serious budget constraints but are not necessary to spur action, for shaming can be very effective by harnessing the power of social pressure and peer monitoring. Through a combination of shaming and subsidies, social marketing can improve sanitation worldwide.

Comment

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It seems unusual for a successful intervention to be based on “shaming”, rather than rewarding positive behaviour. However this was not shaming individuals, but demonstrating to communities their poor hygiene. There were three parts to the intervention. The first was a community walk aimed to draw attention to poor hygiene and to trigger a collective emotional response. The second was “a participatory exercise that sought to identify the spatial distribution of defecation behaviours” and to demonstrate the effects of poor hygiene on the entire village. The third involved determining and discussing the volume of faecal matter accumulated in a village. Poor households received a subsidy for building latrines, costing them only US\$7.50 out of a total cost of US\$50.

Integrated management of childhood illness

Lancet. 2009 Aug 1;374(9687):393-403.

Effect of the Integrated Management of Childhood Illness strategy on childhood mortality and nutrition in a rural area in Bangladesh: a cluster randomised trial.

Arifeen SE, Hoque DM, Akter T, Rahman M, Hoque ME, Begum K, Chowdhury EK, Khan R, Blum LS, Ahmed S, Hossain MA, Siddik A, Begum N, Sadeq-ur Rahman Q, Haque TM, Billah SM, Islam M, Rumi RA, Law E, Al-Helal ZA, Baqui AH, Schellenberg J, Adam T, Moulton LH, Habicht JP, Scherpbier RW, Victora CG, Bryce J, Black RE.

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Abstract

BACKGROUND: WHO and UNICEF launched the Integrated Management of Childhood Illness (IMCI) strategy in the mid-1990s to reduce deaths from diarrhoea, pneumonia, malaria, measles, and malnutrition in children younger than 5 years. We assessed the effect of IMCI on health and nutrition of children younger than 5 years in Bangladesh. **METHODS:** In this cluster randomised trial, 20 first-level government health facilities in the Matlab subdistrict of Bangladesh and their catchment areas (total population about 350 000) were paired and randomly assigned to either IMCI (intervention; ten clusters) or usual services (comparison; ten clusters). All three components of IMCI—health-worker training, health-systems improvements, and family and community activities—were implemented beginning in February, 2002. Assessment included household and health facility surveys tracking intermediate outputs and outcomes, and nutrition and mortality changes in intervention and comparison areas. Primary endpoint was mortality in children aged between 7 days and 59 months. Analysis was by intention to treat. This study is registered, number ISRCTN52793850. **FINDINGS:** The yearly rate of mortality reduction in children younger than 5 years (excluding deaths in first week of life) was similar in IMCI and comparison areas (8.6% vs 7.8%). In the last 2 years of the study, the mortality rate was 13.4% lower in IMCI than in comparison areas (95% CI -14.2 to 34.3), corresponding to 4.2 fewer deaths per 1000 livebirths (95% CI -4.1 to 12.4; $p=0.30$). Implementation of IMCI led to improved health-worker skills, health-system support, and family and community practices, translating into increased care-seeking for illnesses. In IMCI

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areas, more children younger than 6 months were exclusively breastfed (76% vs 65%, difference of differences 10.1%, 95% CI 2.65-17.62), and prevalence of stunting in children aged 24-59 months decreased more rapidly (difference of differences -7.33, 95% CI -13.83 to -0.83) than in comparison areas. INTERPRETATION: IMCI was associated with positive changes in all input, output, and outcome indicators, including increased exclusive breastfeeding and decreased stunting. However, IMCI implementation had no effect on mortality within the timeframe of the assessment.

Comment

In this study in 10 districts in Bangladesh, IMCI proved an effective primary care case management strategy, improving standardized management of common illnesses, and increased health service utilization. However rapid improvement in child survival was seen in the entire study area over 5 years. This was associated with increases in rates of breast feeding, maternal education, sanitation, housing, electricity and mobile phone ownership. In the final 2 years of the study the mortality rate was 13% lower in IMCI than in comparison areas. Although not statistically significant, this would be very substantial if applied over a longer period and across the whole country.

In the 1990s, the introduction of IMCI was initially strongly funded by external donors, with a focus on in-service training for health workers in IMCI case management. Within 10 years, global donor support for IMCI has waned, leaving health departments with a commitment to often complex IMCI programs bolted-on to their MCH programs, often incompletely integrated and now inadequately funded. In many countries, during the early period of strong donor funding of IMCI, little effort went into incorporating IMCI training in schools and colleges of nursing, community health and medicine. For IMCI to be sustained as part of the health culture, program simplification and more support for incorporation into health training colleges and existing MCH systems are essential.

Leishmaniasis

N Engl J Med. 2010 Feb 11;362(6):504-12.

<http://content.nejm.org/cgi/content/full/362/6/504>

Single-dose liposomal amphotericin B for visceral leishmaniasis in India.

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Abstract

BACKGROUND: Some 50% of patients with visceral leishmaniasis (kala-azar) worldwide live in the Indian state of Bihar. Liposomal amphotericin B is an effective treatment when

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administered in short courses. **We wanted to determine whether the efficacy of a single infusion of liposomal amphotericin B was inferior to conventional parenteral therapy, consisting of 15 alternate-day infusions of amphotericin B deoxycholate.** METHODS: In this open-label study, we randomly assigned **412 patients in a 3:1 ratio to receive either liposomal amphotericin B (liposomal-therapy group) or amphotericin B deoxycholate (conventional-therapy group).** Liposomal amphotericin B (at a dose of 10 mg per kilogram of body weight) was given once, and patients were discharged home 24 hours later. Amphotericin B deoxycholate, which was administered in 15 infusions of 1 mg per kilogram, was given every other day during a 29-day hospitalization. We determined the cure rate 6 months after treatment. RESULTS: A total of 410 patients--304 of 304 patients (100%) in the liposomal-therapy group and 106 of 108 patients (98%) in the conventional-therapy group--had apparent cure responses at day 30. **Cure rates at 6 months were similar in the two groups: 95.7% (95% confidence interval [CI], 93.4 to 97.9) in the liposomal-therapy group and 96.3% (95% CI, 92.6 to 99.9) in the conventional-therapy group.** Adverse events in the liposomal-therapy group were infusion-related fever or rigors (in 40%) and increased anemia or thrombocytopenia (in 2%); such events in the conventional-therapy group were fever or rigors (in 64%), increased anemia (in 19%), and hypokalemia (in 2%). Nephrotoxicity or hepatotoxicity developed in no more than 1% of patients in each group. CONCLUSIONS: **A single infusion of liposomal amphotericin B was not inferior to and was less expensive than conventional therapy with amphotericin B deoxycholate.**

Clin Infect Dis. 2009 Sep 15;49(6):914-8.

<http://www.journals.uchicago.edu/doi/pdf/10.1086/605438>

Short-course paromomycin treatment of visceral leishmaniasis in India: 14-day vs 21-day treatment.

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Abstract

BACKGROUND: Treatment of visceral leishmaniasis (VL) is far from satisfactory. There is an urgent need for a therapy that is efficacious, safe, affordable, and of short duration. **METHODS:** A randomized open-label study was conducted to assess the efficacy and safety of 2 regimens of paromomycin administered intramuscularly. Group A received 11 mg/kg/day for 14 days (n = 217) and group B received 11 mg/kg/day for 21 days (n = 112) for the treatment of VL in India. **RESULTS:** Mild grade injection site pain was the most common adverse event. There was no nephrotoxicity, but 4 patients in group A had to discontinue treatment because of grade 3 elevation of hepatic enzymes. Initial cure was observed in 91.2% and 96.4% of patients in group A and group B, respectively. Definitive cure at 6 months of follow up was seen in 82% of patients in group A and 92% of patients in group B by intention-to-treat analysis and in 84.3% of patients in group A and 92.8% of patients in group B by per protocol analysis. **CONCLUSIONS:** Although the cure rate in the group of patients who received the 14-day regimen was not optimal, the results with respect to initial cure were encouraging. Further studies that combine a short course of paromomycin with treatment with another antileishmanial agent are warranted.

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East Mediterr Health J. 2010 Jan;16(1):89-93.

Evaluation of intralesional 0.2% ciprofloxacin as a treatment for cutaneous leishmaniasis.

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Abstract

Although cutaneous leishmaniasis lesions usually heal spontaneously they cause unsightly scarring. This study evaluated a possible new therapy in 38 patients, with 70 lesions, randomly assigned to intralesional injection of ciprofloxacin (0.2%) or intralesional sodium chloride hypertonic solution (7%). After excluding patients who defaulted on treatment, lesions assigned to sodium chloride treatment (n = 21) were completely healed (with or without scarring) in 76.2% of cases, and, when a scar remained, the scar size was reduced 66.0% compared with the original lesion. Lesions assigned to ciprofloxacin (n = 27) showed an 81.5% healing rate with an average scar size reduction of 68.6%. Intralesional 0.2% ciprofloxacin was as effective as hypertonic saline in the treatment of cutaneous leishmaniasis infection.

Malaria

Malaria vaccines

J Infect Dis. 2009 Aug 1;200(3):329-36.

<http://www.journals.uchicago.edu/doi/pdf/10.1086/600119>

Long-term safety and efficacy of the RTS,S/AS02A malaria vaccine in Mozambican children.

Sacarlal J, Aide P, Aponte JJ, Renom M, Leach A, Mandomando I, Lievens M, Bassat Q, Lafuente S, Macete E, Vekemans J, Guinovart C, Sigauque B, Sillman M, Milman J, Dubois MC, Demoitié MA, Thonnard J, Menéndez C, Ballou WR, Cohen J, Alonso PL.

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Abstract

BACKGROUND: We previously reported that the RTS,S/AS02A vaccine had an acceptable safety profile, was immunogenic, and demonstrated efficacy against *Plasmodium falciparum* malaria disease for 21 months. **METHODS:** We conducted a randomized, controlled, phase 2b

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trial of RTS,S/AS02A in 2022 Mozambican children aged 1-4 years. We now report safety results for all randomized subjects and vaccine efficacy (VE) findings for children in the Manhiça area over the 45-month surveillance period. **RESULTS: During the surveillance period, the VE((2.5-45)) (VE over months 2.5-45 of surveillance) against a first or only episode of clinical malaria disease was 30.5% (95% confidence interval [CI], 18.9%-40.4%; P < .001), and the VE((2.5-45)) against all episodes was 25.6% (95% CI, 11.9%-37.1%; P < .001).** When the same period was considered, the VE((2.5-45)) for subjects protected against severe malaria was 38.3% (95% CI, 3.4%-61.3%; P = .045). **At study month 45, the prevalence of P. falciparum was 34% lower in the RTS,S/AS02A group than in the control group (66 [12.2%] of 541 patients vs 101 [18.5%] of 547 patients) (P = .004).** **CONCLUSION:** These results show evidence that RTS,S/AS02A maintained protection during the 45-month surveillance period, and they highlight the feasibility of developing an effective vaccine against malaria. In combination with other malaria-control measures, such a vaccine could greatly contribute to reducing the intolerable global burden of this disease.

PLoS One. 2009 Oct 2;4(10):e7302.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007302>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2750750/?tool=pubmed>

Randomized controlled trial of RTS,S/AS02D and RTS,S/AS01E malaria candidate vaccines given according to different schedules in Ghanaian children.

Owusu-Agyei S, Ansong D, Asante K, Kwarteng Owusu S, Owusu R, Wireko Brobby NA, Dosoo D, Osei Akoto A, Osei-Kwakye K, Adjei EA, Boahen KO, Sylverken J, Adjei G, Sambian D, Apanga S, Kayan K, Vekemans J, Ofori-Anyinam O, Leach A, Lievens M, Demoitie MA, Dubois MC, Cohen J, Ballou WR, Savarese B, Chandramohan D, Gyapong JO, Milligan P, Antwi S, Agbenyega T, Greenwood B, Evans J.

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Abstract

BACKGROUND: The target delivery channel of RTS,S candidate malaria vaccines in malaria-endemic countries in Africa is the World Health Organisation Expanded Program on Immunization. As an Adjuvant System, age de-escalation and schedule selection step, this study assessed 3 schedules of RTS,S/AS01(E) and RTS,S/AS02(D) in infants and young children 5-17 months of age in Ghana. **METHODOLOGY: A Phase II, partially-blind randomized controlled study (blind to vaccine, not to schedule), of 19 months duration was conducted in two (2) centres in Ghana between August 2006 and May 2008.** Subjects were allocated randomly (1:1:1:1:1:1) to one of six study groups at each study site, each defining which vaccine should be given and by which schedule (0,1-, 0,1,2- or 0,1,7-months). For the 0,1,2-month schedule participants received RTS,S/AS01(E) or rabies vaccine at one center and RTS,S/AS01(E) or RTS,S/AS02(D) at the other. For the other schedules at both study sites, they received RTS,S/AS01(E) or RTS,S/AS02(D). The primary outcome measure was the occurrence of serious adverse events until 10 months post dose 1. **RESULTS:** The number of serious adverse events reported across groups was balanced. One child had a simple febrile convulsion,

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which evolved favourably without sequelae, considered to be related to RTS,S/AS01(E) vaccination. Low grade reactions occurred slightly more frequently in recipients of RTS,S/AS than rabies vaccines; grade 3 reactions were infrequent. Less local reactogenicity occurred with RTS,S/AS01(E) than RTS,S/AS02(D). **Both candidate vaccines were highly immunogenic for anti-circumsporozoite and anti-Hepatitis B Virus surface antigen antibodies. Recipients of RTS,S/AS01(E) compared to RTS,S/AS02(D) had higher peak anti-circumsporozoite antibody responses for all 3 schedules. Three dose schedules were more immunogenic than 2 dose schedules.** Area under the curve analyses for anti-circumsporozoite antibodies were comparable between the 0,1,2- and 0,1,7-month RTS,S/AS01(E) schedules. CONCLUSIONS: Both candidate malaria vaccines were well tolerated. Anti-circumsporozoite responses were greater with RTS,S/AS01(E) than RTS,S/AS02(D) and when 3 rather than 2 doses were given. **This study supports the selection of RTS,S/AS01(E) and a 3 dose schedule for further development in children and infants.**

Infect Immun. 2009 Oct;77(10):4502-9. Epub 2009 Aug 3.

<http://iai.asm.org/cgi/reprint/77/10/4502>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2747951/?tool=pubmed>

Plasmodium falciparum-specific cellular immune responses after immunization with the RTS,S/AS02D candidate malaria vaccine in infants living in an area of high endemicity in Mozambique.

Barbosa A, Naniche D, Aponte JJ, Manaca MN, Mandomando I, Aide P, Sacarlal J, Renom M, Lafuente S, Ballou WR, Alonso PL.

Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique.

Abstract

Results from clinical trials in areas where malaria is endemic have shown that immunization with RTS,S/AS02A malaria vaccine candidate induces partial protection in adults and children and cellular effector and memory responses in adults. **For the first time in a malaria vaccine trial, we sought to assess the cell-mediated immune responses to RTS,S antigen components in infants under 1 year of age participating in a clinical phase I/IIb trial of RTS,S/AS02D in Mozambique.** Circumsporozoite protein (CSP)-specific responses were detected in approximately half of RTS,S-immunized infants and included gamma interferon (IFN-gamma), interleukin-2 (IL-2), and combined IL-2/IL-4 responses. The median stimulation indices of cytokine-producing CD4(+) and CD8(+) cells were very low but significantly higher in RTS,S-immunized infants than in infants that received the comparator vaccine. Protection against subsequent malarial infection tended to be associated with a higher percentage of individuals with CSP-specific IL-2 in the supernatant (P = 0.053) and with higher CSP-specific IFN-gamma-producing CD8(+) T-cell responses (P = 0.07). These results report for the first time the detection of malaria-specific cellular immune responses after vaccination of infants less than 1 year of age and pave the way for future field studies of cellular immunity to malaria vaccine candidates.

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PLoS One. 2009 Oct 27;4(10):e7611.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007611>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2763199/?tool=pubmed>

A randomized trial assessing the safety and immunogenicity of AS01 and AS02 adjuvanted RTS,S malaria vaccine candidates in children in Gabon.

Lell B, Agnandji S, von Glasenapp I, Haertle S, Oyakhiromen S, Issifou S, Vekemans J, Leach A, Lievens M, Dubois MC, Demoitie MA, Carter T, Villafana T, Ballou WR, Cohen J, Kremsner PG.

Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon.

Abstract

BACKGROUND: The malaria vaccine candidate antigen RTS,S includes parts of the pre-erythrocytic stage circumsporozoite protein fused to the Hepatitis B surface antigen. Two Adjuvant Systems are in development for this vaccine, an oil-in water emulsion--based formulation (AS02) and a formulation based on liposomes (AS01). **METHODS & PRINCIPAL FINDINGS:** In this Phase II, double-blind study (NCT00307021), **180 healthy Gabonese children aged 18 months to 4 years were randomized to receive either RTS,S/AS01(E) or RTS,S/AS02(D), on a 0-1-2 month vaccination schedule.** The children were followed-up daily for six days after each vaccination and monthly for 14 months. Blood samples were collected at 4 time-points. Both vaccines were well tolerated. Safety parameters were distributed similarly between the two groups. **Both vaccines elicited a strong specific immune response after Doses 2 and 3 with a ratio of anti-CS GMT titers (AS02(D)/AS01(E)) of 0.88 (95% CI: 0.68-1.15) post-Dose 3. After Doses 2 and 3 of experimental vaccines, anti-CS and anti-HBs antibody GMTs were higher in children who had been previously vaccinated with at least one dose of hepatitis B vaccine compared to those not previously vaccinated.** **CONCLUSIONS:** RTS,S/AS01(E) proved similarly as well tolerated and immunogenic as RTS,S/AS02(D), completing an essential step in the age de-escalation process within the RTS,S clinical development plan.

PLoS One. 2009 Oct 26;4(10):e7549.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007549>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2764341/?tool=pubmed>

Safety and immunogenicity of the malaria vaccine candidate MSP3 long synthetic peptide in 12-24 months-old Burkinabe children.

Sirima SB, Tiono AB, Ouédraogo A, Diarra A, Ouédraogo AL, Yaro JB, Ouédraogo E, Gansané A, Bougouma EC, Konaté AT, Kaboré Y, Traoré A, Roma C, Soulama I, Luty AJ, Cousens S, Nébié I.

Randomised trials in child health in developing countries 2009-10

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Abstract

BACKGROUND: A Phase Ia trial in European volunteers of the candidate vaccine merozoite surface protein 3 (MSP3), a Plasmodium falciparum blood stage membrane, showed that it induces biologically active antibodies able to achieve parasite killing in vitro, while a phase Ib trial in semi-immune adult volunteers in Burkina Faso confirmed that the vaccine was safe. The aim of this study was to assess the safety and immunogenicity of this vaccine candidate in children aged 12-24 months living in malaria endemic area of Burkina Faso. **METHODS:** The study was a double-blind, randomized, controlled, dose escalation phase Ib trial, designed to assess the safety, reactogenicity and immunogenicity of three doses of either 15 or 30 microg of MSP3-LSP adsorbed on aluminum hydroxide in 45 children 12 to 24 months of age randomized into three equal groups. Each group received 3 vaccine doses (on days 0, 28 and 56) of either 15 microg of MSP3-LSP, 30 microg of MSP3-LSP or of the Engerix B hepatitis B vaccine. Children were visited at home daily for the 6 days following each vaccination to solicit symptoms which might be related to vaccination. Serious adverse events occurring during the study period (1 year) were recorded. Antibody responses to MSP3-LSP were measured on days 0, 28, 56 and 84. **RESULTS:** All 45 enrolled children received three MSP3 vaccine doses. No serious adverse events were reported. Most of the adverse events reported were mild to moderate in severity. The only reported local symptoms with grade 3 severity were swelling and induration, with an apparently dose related response. All grade 3 adverse events resolved without any sequelae. **Both MSP3 doses regimens were able to elicit high levels of anti-MSP3 specific IgG1 and IgG3 antibodies in the volunteers with very little or no increase in IgG2, IgG4 and IgM classes: i.e. vaccination induced predominantly the isotypes involved in the monocyte-dependent mechanism of P. falciparum parasite-killing.** **CONCLUSION:** Our results support the promise of MSP3-LSP as a malaria vaccine candidate, both in terms of tolerability and of immunogenicity. Further assessment of the efficacy of this vaccine is recommended.

Malar J. 2009 Jul 17;8:163.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720982/?tool=pubmed>

Satisfactory safety and immunogenicity of MSP3 malaria vaccine candidate in Tanzanian children aged 12-24 months.

Lusingu JP, Gesase S, Msham S, Francis F, Lemnge M, Seth M, Sembuche S, Rutta A, Minja D, Segeja MD, Bosomprah S, Cousens S, Noor R, Chilengi R, Druilhe P.

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Abstract

BACKGROUND: Development and deployment of an effective malaria vaccine would complement existing malaria control measures. A blood stage malaria vaccine candidate, Merozoite Surface Protein-3 (MSP3), produced as a long synthetic peptide, has been shown to be safe in non-immune and semi-immune adults. A phase Ib dose-escalating study was

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conducted to assess the vaccine's safety and immunogenicity in children aged 12 to 24 months in Korogwe, Tanzania (ClinicalTrials.gov number: NCT00469651). **METHODS:** This was a double-blind, randomized, controlled, dose escalation phase Ib trial, in which children were given one of two different doses of the MSP3 antigen (15 microg or 30 microg) or a control vaccine (Engerix B). Children were randomly allocated either to the MSP3 candidate malaria vaccine or the control vaccine administered at a schedule of 0, 1, and 2 months. Immunization with lower and higher doses was staggered for safety reasons starting with the lower dose. The primary endpoint was safety and reactogenicity within 28 days post-vaccination. Blood samples were obtained at different time points to measure immunological responses. Results are presented up to 84 days post-vaccination. **RESULTS:** A total of 45 children were enrolled, 15 in each of the two MSP3 dose groups and 15 in the Engerix B group. There were no important differences in reactogenicity between the two MSP3 groups and Engerix B. Grade 3 adverse events were infrequent; only five were detected throughout the study, all of which were transient and resolved without sequelae. No serious adverse event reported was considered to be related to MSP3 vaccine. Both MSP3 dose regimens elicited strong cytophilic IgG responses (subclasses IgG1 and IgG3), the isotypes involved in the monocyte-dependant mechanism of Plasmodium falciparum parasite-killing. The titers reached are similar to those from African adults having reached a state of premunition. Furthermore, vaccination induced seroconversion in all vaccinees. **CONCLUSION: The MSP3 malaria vaccine candidate was safe, well tolerated and immunogenic in children aged 12-24 months living in a malaria endemic community.** Given the vaccine's safety and its induction of cytophilic IgG responses, its efficacy against P. falciparum infection and disease needs to be evaluated in Phase 2 studies.

PLoS One. 2010 Feb 4;5(2):e9041.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0009041>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2816207/?tool=pubmed>

Safety and immunogenicity of an AMA1 malaria vaccine in Malian children: results of a phase 1 randomized controlled trial.

Thera MA, Doumbo OK, Coulibaly D, Laurens MB, Kone AK, Guindo AB, Traore K, Sissoko M, Diallo DA, Diarra I, Kouriba B, Daou M, Dolo A, Baby M, Sissoko MS, Sagara I, Niangaly A, Traore I, Olotu A, Godeaux O, Leach A, Dubois MC, Ballou WR, Cohen J, Thompson D, Dube T, Soisson L, Diggs CL, Takala SL, Lyke KE, House B, Lanar DE, Dutta S, Heppner DG, Plowe CV.

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Abstract

BACKGROUND: The objective was to evaluate the safety and immunogenicity of the AMA1-based malaria vaccine FMP2.1/AS02(A) in children exposed to seasonal falciparum malaria. **METHODOLOGY/PRINCIPAL FINDINGS:** A Phase 1 double blind randomized controlled dose escalation trial was conducted in Bandiagara, Mali, West Africa, a rural town with intense seasonal transmission of Plasmodium falciparum malaria. The malaria vaccine FMP2.1/AS02(A) is a recombinant protein (FMP2.1) based on apical membrane antigen 1 (AMA1) from the 3D7 clone of P. falciparum, formulated in the Adjuvant System AS02(A). The comparator vaccine was a cell-culture rabies virus vaccine (RabAvert). **One hundred**

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healthy Malian children aged 1-6 years were recruited into 3 cohorts and randomized to receive either 10 microg FMP2.1 in 0.1 mL AS02(A), or 25 microg FMP2.1 in 0.25 mL AS02(A), or 50 microg FMP2.1 50 microg in 0.5 mL AS02(A), or rabies vaccine. Three doses of vaccine were given at 0, 1 and 2 months, and children were followed for 1 year. Solicited symptoms were assessed for 7 days and unsolicited symptoms for 30 days after each vaccination. Serious adverse events were assessed throughout the study. Transient local pain and swelling were common and more frequent in all malaria vaccine dosage groups than in the comparator group, but were acceptable to parents of participants. Levels of anti-AMA1 antibodies measured by ELISA increased significantly (at least 100-fold compared to baseline) in all 3 malaria vaccine groups, and remained high during the year of follow up.

CONCLUSION/SIGNIFICANCE: The FMP2.1/AS02(A) vaccine had a good safety profile, was well-tolerated, and induced high and sustained antibody levels in malaria-exposed children. This malaria vaccine is being evaluated in a Phase 2 efficacy trial in children at this site.

Intermittent preventative treatment

Comment

There were 6 IPTi trials published this year. The results included:

Where the prevalence of malaria is low because of better insecticide-treated bed net coverage and other measures, the efficacy of IPTi against clinical malaria is modest. IPTi needs to be considered in the context of widespread distributions of ITNs.

In one large study chlorproguanil-dapsone was associated with higher mortality, although the mechanism is uncertain, haemolysis from G6PD deficiency is a possibility (see also section on treatment of uncomplicated malaria). The preparation of chlorproguanil-dapsone used has been withdrawn.

Mefloquine when used for IPTi is poorly tolerated (high rates of vomiting), and in well children its side effect profile outweighs the modest clinical effectiveness.

In two effectiveness trials, moderate coverage was achieved in Tanzania and high coverage in Ghana, through existing health worker outreach services.

A trial from Gabon confirmed other recent studies findings of no significant rebound effect in the second year of life among IPTi recipients, but a large trial in Tanzania showed IPTi to have only a short term effect, with no protective effect (but no rebound) in the second year of life.

One nested study within an IPTi trial failed to show that the active case finding and treatment of malaria had any effect on stunting.

Being in an IPTi trial – or any RCT - is generally good for you! One study showed much lower mortality among all the participants in an IPTi trial than in the overall population, and another that improved health services provided by the trial may also have benefited children not included living in study villages.

Lancet. 2009 Oct 31;374(9700):1521-32. Epub 2009 Sep 16.

Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial.

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Abstract

BACKGROUND: Administration of sulfadoxine-pyrimethamine at times of vaccination-intermittent preventive treatment in infants (IPTi)-is a promising strategy to prevent malaria. However, rising resistance to this combination is a concern. We investigated a shortacting and longacting antimalarial drug as alternative regimens for IPTi. **METHODS:** We undertook a double-blind, placebo-controlled trial of IPTi in an area of high resistance to sulfadoxine-pyrimethamine at sites of moderate (n=1280 infants enrolled) and low (n=1139) intensity of malaria transmission in Tanzania. Infants aged 8-16 weeks were randomly assigned in blocks of 16 to sulfadoxine (250 mg) plus pyrimethamine (12.5 mg; n=319 in moderate-transmission and 283 in low-transmission sites), chlorproguanil (15 mg) plus dapsone (18.75 mg; n=317 and 285), mefloquine (125 mg; n=320 and 284), or placebo (n=320 and 284), given at the second and third immunisations for diphtheria, pertussis, and tetanus, and for measles. Research team and child were masked to treatment. Recruitment was stopped early at the low-transmission site because of low malaria incidence. The primary endpoint was protective efficacy against all episodes of clinical malaria at 2-11 months of age. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00158574. **FINDINGS:** All randomly assigned infants were analysed. **At the moderate-transmission site, mefloquine had a protective efficacy of 38.1% (95% CI 11.8-56.5, p=0.008) against clinical malaria in infants aged 2-11 months, but neither sulfadoxine-pyrimethamine (-6.7%, -45.9 to 22.0) nor chlorproguanil-dapsone (10.8%, -24.6 to 36.1) had a protective effect. No regimen had any protective efficacy against anaemia or hospital admission. Mefloquine caused vomiting in 141 of 1731 (8%) doses given on day 1 (odds ratio vs placebo 5.50, 95% CI 3.56-8.46). More infants died in the chlorproguanil-dapsone and mefloquine groups (18 and 15, respectively) than in the sulfadoxine-pyrimethamine or placebo groups (eight deaths per group; p=0.05 for difference between chlorproguanil-dapsone and placebo).** **INTERPRETATION:** IPTi with a longacting, efficacious drug such as mefloquine can reduce episodes of malaria in infants in a moderate-transmission setting. IPTi with sulfadoxine-pyrimethamine has no benefit in areas of very high resistance to this combination. The appropriateness of IPTi should be measured by the expected incidence of malaria and the efficacy, tolerability, and safety of the drug.

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Am J Trop Med Hyg. 2010 May;82(5):772-81.

Community effectiveness of intermittent preventive treatment for infants (IPTi) in rural southern Tanzania.

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Abstract

Intermittent preventive treatment of malaria in infants (IPTi) with sulphadoxine-pyrimethamine shows evidence of efficacy in individually randomized, controlled trials. In a large-scale effectiveness study, IPTi was introduced in April 2005 by existing health staff through routine contacts in 12 randomly selected divisions out of 24 in 6 districts of rural southern Tanzania. Coverage and effects on malaria and anemia were estimated through a representative survey in 2006 with 600 children aged 2-11 months. **Coverage of IPTi was 47-76% depending on the definition. Using an intention to treat analysis, parasitemia prevalence was 31% in intervention and 38% in comparison areas (P = 0.06). In a "per protocol" analysis of children who had recently received IPTi, parasite prevalence was 22%, 19 percentage points lower than comparison children (P = 0.01).** IPTi can be implemented on a large scale by existing health service staff, with a measurable population effect on malaria, within 1 year of launch.

PLoS One. 2009 Sep 30;4(9):e7256.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007256>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2748713/?tool=pubmed>

Options for the delivery of intermittent preventive treatment for malaria to children: a community randomised trial.

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Abstract

BACKGROUND: Intermittent preventive treatment for malaria in children (IPTc) is a promising new intervention for the prevention of malaria but its delivery is a challenge. We have evaluated the coverage of IPTc that can be achieved by two different delivery systems in Ghana. **METHODS:** IPTc was delivered by volunteers in six villages (community-based arm) and by health workers at health centres or at Expanded Programme on Immunisation outreach clinics (facility based) in another six communities. The villages were selected randomly and drugs were administered in May, June, September and October 2006. The first dose of a three-dose regimen of amodiaquine plus sulphadoxine-pyrimethamine was administered under supervision to 3-59 month-old children (n = 964) in the 12 study villages; doses for days 2 and 3 were given to parents/guardians to administer at home. **RESULTS:** **The proportion of children who received at least the first dose of 3 or more courses of IPTc was slightly higher in the community based arm (90.5% vs 86.6%; p = 0.059). Completion of the three dose regimen was high and similar with both delivery systems (91.6% and 91.7% respectively).**

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CONCLUSION: Seasonal IPTc delivered through community-based or facility-based systems can achieve a high coverage rate with the support and supervision of the district health management team. However, in order to maximise the impact of IPTc, both delivery systems may be needed in some settings.

Malar J. 2009 Oct 24;8:237.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774335/?tool=pubmed>

Presumptive treatment with sulphadoxine-pyrimethamine versus weekly chloroquine for malaria prophylaxis in children with sickle cell anaemia in Uganda: a randomized controlled trial.

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Abstract

BACKGROUND: Malaria carries high case fatality among children with sickle cell anaemia. In Uganda, chloroquine is used for prophylaxis in these children despite unacceptably high levels of resistance. Intermittent presumptive treatment with sulphadoxine-pyrimethamine (SP) has shown great potential for reducing prevalence of malaria and anaemia among pregnant women and infants. **OBJECTIVE:** To compare the efficacy of monthly SP presumptive treatment, versus weekly chloroquine for malaria prophylaxis in children attending the Sickle Cell Clinic, Mulago Hospital. **METHODS:** **Two hundred and forty two children with sickle cell anaemia were randomized to presumptive treatment with SP or weekly chloroquine for malaria prophylaxis.** Active detection of malaria was made at each weekly visit to the clinic over one month. The primary outcome measure was the proportion of children with one malaria episode at one month follow-up. The secondary outcome measures included malaria-related admissions and adverse effects of the drugs. **RESULTS:** Ninety-three percent (114/122) of the children in the chloroquine group and 94% (113/120) in the SP group completed one month follow up. **SP reduced prevalence of malaria by 50% compared to chloroquine [OR = 0.50, (95% CI 0.26-0.97)]; p = 0.042.** Six percent (7/122) of the children receiving weekly chloroquine had malaria related admissions compared to 2.5% (3/120) on presumptive treatment with SP. No serious drug effects were reported in both treatment groups **CONCLUSION:** **Presumptive treatment with SP was more efficacious than weekly chloroquine in reducing prevalence of malaria in children with sickle cell anaemia.** Continued use of chloroquine for malaria chemoprophylaxis in children with sickle cell anaemia in Uganda does not seem to be justified.

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J Nutr. 2010 Mar;140(3):625-9. Epub 2010 Jan 20.

Active malaria morbidity management has limited impact on height status of preschool Senegalese children.

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Abstract

Although infections contribute to growth faltering in preschool children, malaria prevention seems to have limited impact on height status. In 2002-2003, a malaria intermittent preventive treatment (IPT) trial was conducted in Senegal, including randomly selected preschool children from 11 villages. A rapid decrease in stunting prevalence (from 28.3 to 16.3%; $P < 0.0001$) was reported in both intervention and placebo groups. During this 15-mo period, both groups of children benefited from active detection and prompt treatment of malaria attacks. In this study, we investigated whether management of malaria morbidity could explain the improvement of height status. An anthropometric survey, conducted in September 2004 in the area, included 929 2- to 5-y-old children. Some 539 children, previously included in the 2002-2003 IPT trial, benefited from active malaria morbidity management and formed the malaria trial group. The remaining 390 children constituted the control group. Mean height-for-age and stunting prevalence in September 2004 were compared between groups adjusting for age and mother's activity. Mean height-for-age Z-scores did not differ between trial (-1.17 +/- 0.93) and control children (-1.24 +/- 1.00; $P = 0.25$). Only 36- to 47-mo-old malaria trial children had a lower prevalence of stunting than controls of similar age (19.4 vs. 28.7%; $P = 0.044$). Compared with the usually slow progression of height status related to better living conditions, it seems very likely that the rapid improvement observed among IPT study children resulted from the trial. These findings suggest that improved health services provided by the trial may also have benefited children not included living in study villages.

J Infect Dis. 2009 Dec 1;200(11):1658-61.

<http://www.journals.uchicago.edu/doi/pdf/10.1086/647990>

No rebound of morbidity following intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants in Gabon.

Grobusch MP, Gabor JJ, Aponte JJ, Schwarz NG, Poetschke M, Doernemann J, Schuster K, Koester KB, Profanter K, Borchert LB, Kurth F, Pongratz P, Issifou S, Lell B, Kreamsner PG.

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Abstract

In the context of a trial studying intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants in Lambaréné, Gabon, children aged 18-30 months were followed up after having received their last dose at an age of 15 months. **In the intention-to-treat population, the protective efficacy against all malaria episodes was -18.0 (95% confidence interval, -**

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97.4 to 29.5; $P = .529$). The protective efficacy against first or only anemia episode was -45.3 (95% confidence interval, -234.5 to 36.3; $P=.375$). The protective efficacies were negative and were not statistically significant. These results do not appear to support the concept of a rebound effect after intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants. Clinical trials registration. NCT00167843.

Diagnostic tests

** BMJ. 2010 Mar 5;340:c930. doi: 10.1136/bmj.c930.

http://www.bmj.com/cgi/content/full/340/mar05_1/c930?view=long&pmid=20207689

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2833239/?tool=pubmed>

Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana.

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Abstract

OBJECTIVE: To test in West Africa the impact of rapid diagnostic tests on the prescription of antimalarials and antibiotics both where microscopy is used for the diagnosis of malaria and in clinical (peripheral) settings that rely on clinical diagnosis. **DESIGN:** Randomised, controlled, open label clinical trial. **SETTING:** Four clinics in the rural Dangme West district of southern Ghana, one in which microscopy is used for diagnosis of malaria ("microscopy setting") and three where microscopy is not available and diagnosis of malaria is made on the basis of clinical symptoms ("clinical setting"). **PARTICIPANTS:** Patients with suspected malaria. **Interventions** **Patients were randomly assigned to either a rapid diagnostic test or the current diagnostic method at the clinic (microscopy or clinical diagnosis). A blood sample for a research microscopy slide was taken for all patients.** **MAIN OUTCOME MEASURES:** The primary outcome was the prescription of antimalarials to patients of any age whose double read research slide was negative for malaria. The major secondary outcomes were the correct prescription of antimalarials, the impact of test results on antibiotic prescription, and the correct prescription of antimalarials in children under 5 years. **RESULTS:** Of the 9236 patients screened, 3452 were randomised in the clinical setting and 3811 in the microscopy setting. Follow-up to 28 days was 97.6% (7088/7263). **In the microscopy setting, 722 (51.6%) of the 1400 patients with negative research slides in the rapid diagnostic test arm were treated for malaria compared with 764 (55.0%) of the 1389 patients in the microscopy arm (adjusted odds ratio 0.87, 95% CI 0.71 to 1.1; $P=0.16$). In the clinical setting, 578 (53.9%) of the 1072 patients in the rapid diagnostic test arm with negative research slides were treated for malaria compared with 982 (90.1%) of the 1090 patients with negative slides in the clinical diagnosis arm (odds ratio 0.12, 95% CI 0.04 to 0.38; $P=0.001$).** The use of rapid diagnostic tests led to better targeting of antimalarials and antibiotics in the clinical but not the microscopy

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setting, in both children and adults. There were no deaths in children under 5 years at 28 days follow-up in either arm. **CONCLUSION: Where microscopy already exists, introducing rapid diagnostic tests had limited impact on prescriber behaviour. In settings where microscopy was not available, however, using rapid diagnostic tests led to a significant reduction in the overprescription of antimalarials, without any evidence of clinical harm, and to better targeting of antibiotics.**

Comment

This is an important study showing that RDTs can be interpreted correctly and acted upon by health workers, and this can reduce unnecessary prescribing of antimalarials. However this only occurs to a significant extent in settings which formerly relied upon clinical features (i.e. fever) for a diagnosis of malaria. This study provides encouragement that the withholding of antimalarials when the RDT is negative is not dangerous, as there was no evidence of increased rates of repeated presentation or mortality when an RDT was used. In settings where microscopy is available, RDTs have little effect on prescribing.

Insecticide treated material

Malar J. 2010 Mar 24;9:84.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858215/?tool=pubmed>

Evaluation of Interceptor long-lasting insecticidal nets in eight communities in Liberia.

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Abstract

BACKGROUND: By 2008, the WHO Pesticide Evaluation Scheme (WHOPES) recommended five long-lasting insecticidal nets (LLINs) for the prevention of malaria: Olyset((R)), PermaNet 2.0((R)), Netprotect((R)), Duranet((R)) and Interceptor((R)). Field information is available for both Olyset(R) and PermaNet((R)), with limited data on the newer LLINs. To address this gap, a field evaluation was carried out to determine the acceptability and durability of Interceptor((R)) LLINs. **METHODS:** A one-year prospective field study was conducted in eight rural returnee villages in Liberia. **Households were randomized to receive Interceptor((R)) LLINs or conventionally treated nets (CTNs).** Primary outcomes were levels of residual alpha-cypermethrin measured by HPLC and participant utilization/acceptability of the ITNs. **RESULTS:** A total of 398 nets were analysed for residual alpha-cypermethrin. The median baseline concentrations of insecticide were 175.5 mg/m² for the Interceptor((R)) LLIN and 21.8 mg/m² for the CTN. Chemical residue loss after a one year follow-up period was 22% and 93% respectively. Retention and utilization of nets remained high (94%) after one year, irrespective of type, while parasitaemia prevalence decreased from 29.7% at baseline to 13.6% during the

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follow up survey ($p = < 0.001$). Interview and survey data show perceived effectiveness of ITNs was just as important as other physical attributes in influencing net utilization. **CONCLUSION:** Interceptor((R)) LLINs are effective and desirable in rural communities in Liberia. Consideration for end user preferences should be incorporated into product development of all LLINs in the future, in order to achieve optimum retention and utilization.

Acta Trop. 2009 Nov;112(2):181-7. Epub 2009 Aug 6.

Efficacy of permethrin treated long-lasting insecticidal nets on malaria transmission and observations on the perceived side effects, collateral benefits and human safety in a hyperendemic tribal area of Orissa, India.

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Abstract

Studies were conducted on the efficacy of Olyset nets—a long-lasting insecticidal net (LLIN) factory treated with 2% (w/w) permethrin on malaria transmission in an area under the influence of pyrethroid susceptible vector species *Anopheles culicifacies* and *A. fluviatilis* in Sundargarh District, Orissa, India. The study area comprised 22 villages that were randomized into three clusters and designated as Olyset net, untreated net, and no net area. Malaria incidence in the study population was measured through longitudinal active surveillance at fortnightly intervals. **There was a reduction of 65-70% in malaria incidence in Olyset net area as compared to the control areas.** The attack rate of *Plasmodium falciparum* or number of episodes per person per year in different age groups also showed significant reduction in Olyset net area as compared to untreated net and no net areas. Cross-sectional point prevalence surveys showed 45.7% reduction of malaria prevalence in Olyset net users, whereas there was an increase of 33.3% and 51% in untreated net and no net villages respectively. The compliance rate of Olyset net usage in the study population was 80-98% during different months, whereas it was between 70% and 90% for untreated nets. There were minimal complains of skin irritation (4%), itching (8%) and eye irritation (1.2%). However, these effects were only transitory in nature lasting for few hours of the first usage. Olyset nets also provided collateral benefits in terms of relief not only from mosquitoes and malaria but also from other household pests such as head lice, bed bugs, cockroaches, ants and houseflies. The Olyset nets were found to be safe to humans as no adverse event was recorded in the net users that can be attributed to the use of net. The study showed that Olyset nets are effective personal protection tool that can be used in a community based intervention programme.

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Bull World Health Organ. 2009 Sep;87(9):655-65.

<http://www.scielosp.org/pdf/bwho/v87n9/v87n9a09.pdf>

Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial.

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Abstract

OBJECTIVE: To assess the contributions of both microbial larvicides and insecticide-treated nets (ITNs) in terms of reducing malaria incidence in an integrated vector management programme in an area moderately endemic for malaria in the western Kenyan highlands.

METHODS: A pre-post, control group design was used. Larval and adult vector populations were surveyed weekly in six separate valley communities. The incidence of Plasmodium infections in children 6 months to 13 years of age was measured during the long and short rainy seasons each year. Baseline data were collected for 17 months, after which Bacillus-based larvicides were applied weekly to aquatic habitats in three of the valleys for another 19 months. At around the same time the larviciding was initiated, ITNs were introduced gradually into all study communities by the National Malaria Control Programme. The effect of larviciding, ITNs and other determinants of malaria risk was assessed by means of generalized estimating equations. **FINDINGS:** **The risk of acquiring new parasite infections in children was substantially and independently reduced by ITN use (odds ratio, OR: 0.69; 95% confidence interval, CI: 0.48-0.99) and larvicide application (OR: 0.44; 95% CI: 0.23-0.82),** after adjusting for confounders. **CONCLUSION:** Vector control with microbial larvicides enhanced the malaria control achieved with ITNs alone. Anti-larval measures are a promising complement to ITN distribution in the economically important highland areas and similar transmission settings in Africa.

Comment

This is an important study which targets two phases of the vector life-cycle: the adult forms (addressed by ITN use) and the larval form. The larvicides used in this study were commercial strains of Bacillus sphaericus or B. thuringiensis var. israelensis, applied as water-dispersible granulates to all water bodies at weekly intervals. Both ITNs and larvicides had independent and substantial effects on parasitaemia rates.

Other preventative strategies

Cochrane Database Syst Rev. 2010 Apr 14;4:CD006657.

Indoor residual spraying for preventing malaria.

Pluess B, Tanser FC, Lengeler C, Sharp BL.

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Abstract

BACKGROUND: Primary malaria prevention on a large scale depends on two vector control interventions: indoor residual spraying (IRS) and insecticide-treated mosquito nets (ITNs). Historically, IRS has reduced malaria transmission in many settings in the world, but the health effects of IRS have never been properly quantified. This is important, and will help compare IRS with other vector control interventions. **OBJECTIVES:** To quantify the impact of IRS alone, and to compare the relative impacts of IRS and ITNs, on key malariological parameters. **SEARCH STRATEGY:** We searched the Cochrane Infectious Diseases Group Specialized Register (September 2009), CENTRAL (The Cochrane Library 2009, Issue 3), MEDLINE (1966 to September 2009), EMBASE (1974 to September 2009), LILACS (1982 to September 2009), mRCT (September 2009), reference lists, and conference abstracts. We also contacted researchers in the field, organizations, and manufacturers of insecticides (June 2007). **SELECTION CRITERIA:** Cluster randomized controlled trials (RCTs), controlled before-and-after studies (CBA) and interrupted time series (ITS) of IRS compared to no IRS or ITNs. Studies examining the impact of IRS on special groups not representative of the general population, or using insecticides and dosages not recommended by the World Health Organization (WHO) were excluded. **DATA COLLECTION AND ANALYSIS:** Two authors independently reviewed trials for inclusion. Two authors extracted data, assessed risk of bias and analysed the data. Where possible, we adjusted confidence intervals (CIs) for clustering. Studies were grouped into those comparing IRS with no IRS, and IRS compared with ITNs, and then stratified by malaria endemicity. **MAIN RESULTS:** IRS versus no IRS
Stable malaria (entomological inoculation rate (EIR) > 1): In one RCT in Tanzania IRS reduced re-infection with malaria parasites detected by active surveillance in children following treatment; protective efficacy (PE) 54%. In the same setting, malaria case incidence assessed by passive surveillance was marginally reduced in children aged one to five years; PE 14%, but not in children older than five years (PE -2%). In the IRS group, malaria prevalence was slightly lower but this was not significant (PE 6%), but mean haemoglobin was higher (mean difference 0.85 g/dL). In one CBA trial in Nigeria, IRS showed protection against malaria prevalence during the wet season (PE 26%; 95% CI 20 to 32%) but not in the dry season (PE 6%; 95% CI -4 to 15%). In one ITS in Mozambique, the prevalence was reduced substantially over a period of 7 years (from 60 to 65% prevalence to 4 to 8% prevalence; the weighted PE before-after was 74% (95% CI 72 to 76%).
Unstable malaria (EIR < 1): In two RCTs, IRS reduced the incidence rate of all malaria infections; PE 31% in India, and 88% (95% CI 69 to 96%) in Pakistan. By malaria species, IRS also reduced the incidence of *P. falciparum* (PE 93%, 95% CI 61 to 98% in Pakistan) and *P. vivax* (PE 79%, 95% CI 45 to 90% in Pakistan); There were similar impacts on malaria prevalence for any infection: PE 76% in Pakistan; PE 28% in India. When looking separately by parasite species, for *P. falciparum* there was a PE of 92% in Pakistan and 34% in India; for *P. vivax* there was a PE of 68% in Pakistan and no impact demonstrated in India (PE of -2%).
IRS versus Insecticide Treated Nets (ITNs)
Stable malaria (EIR > 1): Only one RCT was done in an area of stable transmission (in Tanzania). When comparing parasitological re-infection by active surveillance after treatment in short-term cohorts, ITNs appeared better, but it was likely not to be significant as the unadjusted CIs approached 1 (risk ratio IRS:ITN = 1.22). When the incidence of malaria episodes was measured by passive case detection, no difference was found in children aged one to five years (risk ratio = 0.88, direction in favour of IRS). No difference was found for malaria prevalence or haemoglobin.
Unstable malaria (EIR < 1): Two studies; for incidence and prevalence, the malaria rates were higher in the IRS group compared to the ITN group in one study. Malaria incidence was higher in the IRS arm in India (risk ratio IRS:ITN = 1.48) and in South Africa (risk ratio 1.34 but the cluster unadjusted CIs included 1). For malaria

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prevalence, ITNs appeared to give better protection against any infection compared to IRS in India (risk ratio IRS:ITN = 1.70) and also for both *P. falciparum* (risk ratio IRS:ITN = 1.78) and *P. vivax* (risk ratio IRS:ITN = 1.37). **AUTHORS' CONCLUSIONS:** Historical and programme documentation has clearly established the impact of IRS. However, the number of high-quality trials are too few to quantify the size of effect in different transmission settings. The evidence from randomized comparisons of IRS versus no IRS confirms that IRS reduces malaria incidence in unstable malaria settings, but randomized trial data from stable malaria settings is very limited. Some limited data suggest that ITN give better protection than IRS in unstable areas, but more trials are needed to compare the effects of ITNs with IRS, as well as to quantify their combined effects.

Lancet. 2009 Sep 19;374(9694):998-1009. Epub 2009 Sep 3.

Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial.

Kirby MJ, Ameh D, Bottomley C, Green C, Jawara M, Milligan PJ, Snell PC, Conway DJ, Lindsay SW.

Science Laboratories, Durham University, Durham, UK.

Abstract

BACKGROUND: House screening should protect people against malaria. We assessed whether two types of house screening--full screening of windows, doors, and closing eaves, or installation of screened ceilings--could reduce house entry of malaria vectors and frequency of anaemia in children in an area of seasonal malaria transmission. **METHODS:** During 2006 and 2007, 500 occupied houses in and near Farafenni town in The Gambia, an area with low use of insecticide-treated bednets, were **randomly assigned to receive full screening, screened ceilings, or no screening (control)**. Randomisation was done by computer-generated list, in permuted blocks of five houses in the ratio 2:2:1. **Screening was not treated with insecticide.** Exposure to mosquitoes indoors was assessed by fortnightly light trap collections during the transmission season. Primary endpoints included the number of female *Anopheles gambiae* sensu lato mosquitoes collected per trap per night. Secondary endpoints included frequency of anaemia (haemoglobin concentration <80 g/L) and parasitaemia at the end of the transmission season in children (aged 6 months to 10 years) who were living in the study houses. Analysis was by modified intention to treat (ITT), including all randomised houses for which there were some outcome data and all children from those houses who were sampled for haemoglobin and parasitaemia. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN51184253. **FINDINGS:** 462 houses were included in the modified ITT analysis (full screening, n=188; screened ceilings, n=178; control, n=96). The mean number of *A. gambiae* caught in houses without screening was 37.5 per trap per night (95% CI 31.6-43.3), compared with 15.2 (12.9-17.4) in houses with full screening (ratio of means 0.41, 95% CI 0.31-0.54; p<0.0001) and 19.1 (16.1-22.1) in houses with screened ceilings (ratio 0.53, 0.40-0.70; p<0.0001). **755 children completed the study, of whom 731 had complete clinical and covariate data and were used in the analysis of clinical outcomes. 30 (19%) of 158 children from control houses had anaemia, compared with 38 (12%) of 309 from houses with full screening (adjusted odds ratio [OR] 0.53, 95% CI 0.29-0.97; p=0.04), and 31 (12%) of 264**

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from houses with screened ceilings (OR 0.51, 0.27-0.96; p=0.04). Frequency of parasitaemia did not differ between intervention and control groups. INTERPRETATION: House screening substantially reduced the number of mosquitoes inside houses and could contribute to prevention of anaemia in children.

Treatment of uncomplicated malaria

The studies are separated according to different drugs being tested, but there is a lot of overlap, as more than one drug combination is being tested.

Studies testing Artemether-Lumefantrine

Lancet. 2010 Apr 24;375(9724):1457-67.

Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated Plasmodium falciparum malaria: a randomised non-inferiority trial.

Tshefu AK, Gaye O, Kayentao K, Thompson R, Bhatt KM, Sesay SS, Bustos DG, Tjitra E, Bedu-Addo G, Borghini-Fuhrer I, Duparc S, Shin CS, Fleckenstein L; Pyronaridine-artesunate Study Team.

Kokolomami J, Yumva NN, Faye B, Ndiaye JL, Guindo N, Djimde M, Enosse S, Kimani J, Bojang K, de los Reyes L, Feliciano-Rivera AV, Siswantoro H, Purnama A, Holsen L, Djimde A, Doumbo OK, Niangaly M, Arnaldo P, Langa J, Chicumbe S, Matandalasse MP, Baldeh I, Belai G, Asante D, Choosakulchart P, Arbe-Barnes S, Didillon E, Mulder A, Oeuvray C, Marti H, Beck HP, Allen S, Miller R, Craft JC, Wignall FS, Saulay M, Demange A.

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Abstract

BACKGROUND: There is a need for new artemisinin-based combination therapies that are convenient, effective, and safe. We compared the efficacy and safety of pyronaridine-artesunate with that of artemether-lumefantrine for treatment of uncomplicated *P falciparum* malaria. **METHODS:** This phase 3, parallel-group, double-blind, randomised, non-inferiority trial was undertaken in seven sites in Africa and three sites in southeast Asia. In a double-dummy design, **patients aged 3-60 years with uncomplicated *P falciparum* malaria were randomly assigned in a 2:1 ratio to receive pyronaridine-artesunate once a day or artemether-lumefantrine twice a day, orally for 3 days, plus respective placebo.** Randomisation was done by computer-generated randomisation sequence in blocks of nine by study centre. Intervention tablets contained 180 mg pyronaridine and 60 mg artesunate; control tablets

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contained 20 mg artemether and 120 mg lumefantrine. Both treatments were given according to bodyweight. **The primary efficacy outcome was PCR-corrected adequate clinical and parasitological response (ACPR) rate at day 28 in the per-protocol population.** Non-inferiority was shown if the lower limit of the two-sided 95% CI for the difference between groups was greater than -5%. This study is registered with ClinicalTrials.gov, number NCT00422084. **FINDINGS:** 1272 patients were randomly assigned to treatment (pyronaridine-artesunate, n=849; artemether-lumefantrine, n=423). The per-protocol population consisted of 784 patients in the pyronaridine-artesunate group and 386 patients in the artemether-lumefantrine group. PCR-corrected ACPR rate at day 28 was 99.5% (780 patients; 95% CI 98.7-99.9) in the pyronaridine-artesunate group and 99.2% (383 patients; 95% CI 97.7-99.8) in the artemether-lumefantrine group (treatment difference 0.3%, 95% CI -0.7 to 1.8; p=0.578). There were 509 (60.0%) adverse events in 849 patients assigned to pyronaridine-artesunate and 241 (57.0%) in 423 patients assigned to artemether-lumefantrine. The most frequent drug-related adverse event was eosinophilia (pyronaridine-artesunate, 53 events [6.2%]; artemether-lumefantrine 24 events [5.7%]). 21 (2.5%) patients in the pyronaridine-artesunate group and seven (1.7%) in the artemether-lumefantrine group discontinued study drugs or were withdrawn from the study. Mild and transient increases in alanine aminotransferase and aspartate aminotransferase concentrations were seen in the pyronaridine-artesunate group but not in the artemether-lumefantrine group. **INTERPRETATION: Efficacy of pyronaridine-artesunate was non-inferior to that of artemether-lumefantrine for treatment of uncomplicated falciparum malaria.** Pyronaridine-artesunate should be considered for inclusion in malaria treatment programmes.

BMJ. 2009 Jul 21;339:b2763. doi: 10.1136/bmj.b2763.

http://www.bmj.com/cgi/content/full/339/jul21_1/b2763?view=long&pmid=19622553

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2714631/?tool=pubmed>

Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial.

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Abstract

OBJECTIVE: To compare the effectiveness of oral quinine with that of artemether-lumefantrine in treating uncomplicated malaria in children. **DESIGN:** Randomised, open label effectiveness study. **SETTING:** Outpatient clinic of Uganda's national referral hospital in Kampala. **PARTICIPANTS:** 175 children aged 6 to 59 months with uncomplicated malaria. **INTERVENTIONS:** Participants were randomised to receive oral quinine or artemether-lumefantrine administered by care givers at home. **MAIN OUTCOME MEASURES:** Primary outcomes were parasitological cure rates after 28 days of follow-up unadjusted and adjusted by genotyping to distinguish recrudescence from new infections. Secondary outcomes were

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adherence to study drug, presence of gametocytes, recovery of haemoglobin concentration from baseline at day 28, and safety profiles. **RESULTS:** Using survival analysis the cure rate unadjusted by genotyping was 96% for the artemether-lumefantrine group compared with 64% for the quinine group (hazard ratio 10.7, 95% confidence interval 3.3 to 35.5, $P=0.001$). In the quinine group 69% (18/26) of parasitological failures were due to recrudescence compared with none in the artemether-lumefantrine group. The mean adherence to artemether-lumefantrine was 94.5% compared with 85.4% to quinine ($P=0.0008$). Having adherence levels of 80% or more was associated with a decreased risk of treatment failure (0.44, 0.19 to 1.02, $P=0.06$). Adverse events did not differ between the two groups. **CONCLUSIONS: The effectiveness of a seven day course of quinine for the treatment of uncomplicated malaria in Ugandan children was significantly lower than that of artemether-lumefantrine.** These findings question the advisability of the recommendation for quinine therapy for uncomplicated malaria in Africa.

Malar J. 2010 Feb 19;9:56.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834703/?tool=pubmed>

Efficacy of non-artemisinin- and artemisinin-based combination therapies for uncomplicated falciparum malaria in Cameroon.

Whegang SY, Tahar R, Foumane VN, Soula G, Gwét H, Thalabard JC, Basco LK.

Unité de Recherche 77 Paludologie Afro-tropicale, Institut de Recherche pour le Développement (IRD) and Laboratoire de Recherche sur le Paludisme, Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale (OCEAC), BP 288, Yaoundé, Cameroon.

Abstract

BACKGROUND: The use of drug combinations, including non-artemisinin-based and artemisinin-based combination therapy (ACT), is a novel strategy that enhances therapeutic efficacy and delays the emergence of multidrug-resistant *Plasmodium falciparum*. Its use is strongly recommended in most sub-Saharan African countries, namely Cameroon, where resistance to chloroquine is widespread and antifolate resistance is emerging. **METHODS:** Studies were conducted in Cameroonian children with acute uncomplicated *P. falciparum* malaria according to the standard World Health Organization protocol at four sentinel sites between 2003 and 2007. A total of 1,401 children were enrolled, of whom 1,337 were assigned to randomized studies and 64 were included in a single non-randomized study. The proportions of adequate clinical and parasitological response (PCR-uncorrected on day 14 and PCR-corrected on day 28) were the primary endpoints to evaluate treatment efficacy on day 14 and day 28. The relative effectiveness of drug combinations was compared by a multi-treatment Bayesian random-effect meta-analysis. **FINDINGS:** The results based on the meta-analysis suggested that artesunate-amodiaquine (AS-AQ) is as effective as other drugs (artesunate-sulphadoxine-pyrimethamine [AS-SP], artesunate-chlorproguanil-dapsone [AS-CD], artesunate-mefloquine [AS-MQ], dihydroartemisinin-piperaquine [DH-PP], artemether-lumefantrine [AM-LM], amodiaquine, and amodiaquine-sulphadoxine-pyrimethamine [AQ-SP]). AM-LM appeared to be the most effective with no treatment failure due to recrudescence, closely followed by DH-PP. **CONCLUSION:** Although AM-LM requires six doses, rather than three

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doses for other artemisinin-based combinations, it has potential advantages over other forms of ACT. Further studies are needed to evaluate the clinical efficacy and tolerance of these combinations in different epidemiological context.

Malar J. 2010 Feb 11;9:48.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2833168/?tool=pubmed>

Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania.

Kabanywany AM, Lengeler C, Kasim P, King'eng'ena S, Schlienger R, Mulure N, Genton B.

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Abstract

BACKGROUND: Controlled clinical trials have shown that a six-dose regimen of artemether-lumefantrine (AL) therapy for uncomplicated *Plasmodium falciparum* malaria results in cure rates >95% with good tolerability. **MATERIALS AND METHODS:** A prospective study was carried out to document the adherence to and acceptability of AL administration. This was undertaken in the context of the ALIVE study, a prospective, community-based, observational study in a rural, malaria-endemic area of Tanzania. Following microscopic confirmation of *P. falciparum* infection, the first AL dose was taken under supervision, with the subsequent five doses taken unsupervised at home. Patients were randomized to receive a home-based assessment close to the scheduled time for one of the unsupervised doses, but were blinded to which follow-up visit they had been allocated. A structured questionnaire was administered by trained staff and AL consumption was confirmed by inspection of blister packs. **RESULTS:** A total of 552 patients were recruited of whom 352 (63.8%) were <13 years old. The randomization process allocated 112, 109, 110, 100 and 111 patients to a follow-up visit after doses 2, 3, 4, 5 and 6, respectively. For dose 2, 92.0% of patients (103/112) correctly took AL at 8 +/- 1 hours after dose 1. The remaining doses were taken within four hours of the correct time in 87-95% of cases. Nine patients (1.7%) missed one dose. Blister packs were available for inspection in 548 of cases (99.3%) and confirmed patient-reported data that the previous dose had been administered. Nearly all patients took AL with water (549/552 [99.5%]). Two patients (0.4%) took the drug with food. The dosing pictogram and clustering of tablets within the blister packs was considered helpful by 91.8% and 100.0% of patients, respectively. **Overall, 87.1% of patients (481/552) found AL easier to take/administer than sulphadoxine-pyrimethamine (SP) and 87.7% (484/552) believed that AL was more effective than SP.** **DISCUSSION:** Factors contributing to adherence were likely to be helpful packaging, pictorial dosing instructions and patients' conviction that AL is effective. **CONCLUSION:** Adherence to the dosing regimen and timing of AL administration was very good.

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Malar J. 2009 Jul 3;8:148.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2714523/?tool=pubmed>

A comparative, randomized clinical trial of artemisinin/naphtoquine twice daily one day versus artemether/lumefantrine six doses regimen in children and adults with uncomplicated falciparum malaria in Côte d'Ivoire.

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Abstract

BACKGROUND: Drug resistance in *Plasmodium falciparum* poses a major threat to malaria control. Combination anti-malarial therapy, including artemisinins, has been advocated to improve efficacy and limit the spread of resistance. The fixed combination of oral artemether-lumefantrine (AL) is highly effective and well-tolerated. Artemisinin/naphtoquine (AN) is a fixed-dose ACT that has recently become available in Africa. The objectives of the study were to compare the efficacy and safety of AN and AL for the treatment of uncomplicated falciparum malaria in a high transmission-intensity site in Ivory Coast. **METHODS:** We enrolled 122 participants aged 6 months or more with uncomplicated falciparum malaria. **Participants were randomized to receive either artemisinin/naphtoquine or artemether/lumefantrine** with variable dose according to their weight. Primary endpoints were the risks of treatment failure within 28 days, either unadjusted or adjusted by genotyping to distinguish recrudescence from new infection. **RESULTS:** Among 125 participants enrolled, 123 (98.4%) completed follow-up. **Clinical evaluation of the 123 participants showed that cumulative PCR-uncorrected cure rate on day 28 was 100% for artemisinin/naphtoquine and 98.4% for artemether/lumefantrine.** Both artemisinin-based combinations effected rapid fever and parasite clearance. **INTERPRETATION:** These data suggest that Arco could prove to be suitable for use as combination antimalarial therapy. Meanwhile, pharmacokinetic studies and further efficacy assessment should be conducted before its widespread use can be supported.

Trop Med Int Health. 2010 Apr;15(4):434-41. Epub 2010 Feb 17.

The effect of food consumption on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablets (Coartem) for acute uncomplicated Plasmodium falciparum malaria.

Borrmann S, Sallas WM, Machevo S, González R, Björkman A, Mårtensson A, Hamel M, Juma E, Peshu J, Ogutu B, Djimdé A, D'Alessandro U, Marrast AC, Lefèvre G, Kern SE.

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Abstract

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OBJECTIVES: Artemether-lumefantrine (AL) is first-line treatment for uncomplicated malaria in many African countries. Concomitant food consumption may affect absorption of lumefantrine but data in the most important target population, i.e. children, are lacking. Therefore, we evaluated the effect of food intake on oral lumefantrine bioavailability in African children with malaria. **METHODS:** In a randomised, investigator-blinded, multicentre phase III efficacy trial, 899 infants and children with acute uncomplicated Plasmodium falciparum malaria received six doses of AL according to body weight over 3 days either as crushed tablets (Coartem) or as dispersible tablets. Single blood samples were obtained for lumefantrine plasma concentration determination in a subset of 621 patients, and a two-compartment pharmacokinetic model was constructed. **RESULTS:** **The mean observed lumefantrine plasma concentration for crushed tablet and dispersible tablet, respectively, was 100% and 55% higher with a concomitant meal at the time of dose intake than when taken alone. Similarly, consumption of milk (the most common meal) increased model-estimated lumefantrine bioavailability by 57% (90% CI: 29-96%) with crushed tablets and 65% (90% CI: 28-109%) with dispersible tablets compared to no food.** The 28-day PCR-corrected cure rate (primary study endpoint) in the evaluable population was 582/587 [99.1% (95% CI: 98.0-99.7%)] and was not related to food intake. **CONCLUSIONS:** AL was highly efficacious. **Concomitant food intake increased lumefantrine absorption in children with malaria.**

Trop Med Int Health. 2010 May;15(5):608-13. Epub 2010 Mar 1.

Efficacy and tolerability of artesunate-amodiaquine (Camoquin plus) versus artemether-lumefantrine (Coartem) against uncomplicated Plasmodium falciparum malaria: multisite trial in Senegal and Ivory Coast.

Faye B, Offianan AT, Ndiaye JL, Tine RC, Touré W, Djoman K, Sylla K, Ndiaye PS, Penali L, Gaye O.

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Abstract

OBJECTIVE: To compare, in a phase IV trial, the efficacy and tolerability of artesunate-amodiaquine (Camoquin plus) dosed at 300 and 600 mg of amodiaquine per tablet to artemether-lumefantrine (Coartem) for the treatment of Plasmodium falciparum uncomplicated malaria in Ivory Coast and Senegal. **METHOD:** Multisite, randomised, open-labelled study in patients over the age of 7 years. The primary endpoint for efficacy was adequate clinical and parasitological response (ACPR) at day 28. The secondary endpoints were fever and parasite clearance and gametocyte carriage in each treatment group. Drug tolerability was assessed comparing adverse events and modification of biological parameters between D0 and D7. Data were analysed on an intention-to-treat and per protocol basis. **RESULTS:** We included 322 patients; 316 patients completed the monitoring to D28 (155 in AS + AQ group and 161 in AL group). In ITT analysis, an ACPR corrected rate of 97.4% was observed in AS + AQ group versus 97% in AL group (P = 0.99). No parasite recrudescence was observed in AS + AQ arm. **All patients in both groups had a fever and parasite clearance at D2. Gametocytes had disappeared by D14 in the AL group and by D21 in the AS + AQ group. No serious adverse events were observed.** Minor adverse events were significantly more frequent in the

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AS + AQ arm. Biological parameters between D0 and D7 did not show any significant statistical variations except for anaemia. CONCLUSION: This study demonstrates the efficacy and tolerability of AS + AQ for uncomplicated *Plasmodium falciparum* malaria treatment in African patients over the age of 7 years.

Malar J. 2009 Aug 26;8:204.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2744923/?tool=pubmed>

Measurement of adherence, drug concentrations and the effectiveness of artemether-lumefantrine, chlorproguanil-dapsone or sulphadoxine-pyrimethamine in the treatment of uncomplicated malaria in Malawi.

Bell DJ, Wootton D, Mukaka M, Montgomery J, Kayange N, Chimpeni P, Hughes DA, Molyneux ME, Ward SA, Winstanley PA, Lalloo DG.

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Abstract

BACKGROUND: Sulphadoxine-pyrimethamine (SP) is the only single dose therapy for uncomplicated malaria, but there is widespread resistance. At the time of this study, artemether-lumefantrine (AL) and chlorproguanil-dapsone (CPD), both multi-dose regimes, were considered possible alternatives to SP in Malawi. The aim of this study was to investigate the impact of poor adherence on the effectiveness of AL and CPD. **METHODS: Children > or =12 months and adults with uncomplicated malaria were randomized to receive AL, CPD or SP.** Adherence was measured using a questionnaire and electronic monitoring devices, MEMS, pill bottles that recorded the date and time of opening. Day-7 plasma dapsone or lumefantrine concentrations were measured to examine their relationship with adherence and clinical response. **RESULTS:** 841 patients were recruited. **The day-28 adequate clinical and parasitological response (ACPR) rates, using intention to treat analysis (missing data treated as failure), were AL 85.2%, CPD 63.7% and SP 50%.** ACPR rates for AL were higher than CPD or SP on days 28 and 42 ($p < \text{or} = 0.002$ for all comparisons). CPD was more effective than SP on day-28 ($p = 0.01$), but not day-42. Very high adherence was reported using the questionnaire, 100% for AL treated patients and 99.2% for the CPD group. Only three CPD participants admitted missing any doses. 164/181 (90.6%) of CPD treated patients took all their doses out of the MEMS container and they were more likely to have a day-28 ACPR than those who did not take all their medication out of the container, $p = 0.024$. Only 7/87 (8%) AL treated patients did not take all of their doses out of their MEMS container and none had treatment failure. Median day-7 dapsone concentrations were higher in CPD treated patients with ACPR than in treatment failures, $p = 0.012$. There were no differences in day-7 dapsone or lumefantrine concentrations between those who took all their doses from the MEMS container and those who did not. A day-7 lumefantrine concentration reported to be predictive of AL treatment failure in Thailand was not useful in this population; only one of 16 participants with a concentration below this threshold (175 ng/ml) had treatment failure. **CONCLUSION:** This study provides reassurance of the effectiveness of AL, even with unsupervised dosing, as it is rolled out across sub-Saharan Africa. Self-reported adherence appears to be an unreliable measure of adherence in this population.

Studies testing Dihydroartemisinin-piperaquine

Comment

This year 3 studies involving 8 African countries found that dihydroartemisinin-piperaquine is as safe and effective as artemether-lumefantrine (AL) in the treatment of uncomplicated falciparum malaria, and 2 of these studies showed lower rates of recurrence at 28 and 42 days with DP, suggesting a longer term prophylactic effect than with AL. One study showed DP was effective in the treatment of vivax malaria (see section Treatment of vivax malaria)

PLoS One. 2009 Nov 17;4(11):e7871.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007871>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776302/?tool=pubmed>

Dihydroartemisinin-piperaquine and artemether-lumefantrine for treating uncomplicated malaria in African children: a randomised, non-inferiority trial.

Bassat Q, Mulenga M, Tinto H, Piola P, Borrmann S, Menéndez C, Nambozi M, Valéa I, Nabasumba C, Sasi P, Bacchieri A, Corsi M, Ubben D, Talisuna A, D'Alessandro U.

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Abstract

BACKGROUND: Artemisinin combination therapies (ACTs) are currently the preferred option for treating uncomplicated malaria. Dihydroartemisinin-piperaquine (DHA-PQP) is a promising fixed-dose ACT with limited information on its safety and efficacy in African children. **METHODOLOGY/PRINCIPAL FINDINGS:** The non-inferiority of DHA-PQP versus artemether-lumefantrine (AL) in children 6-59 months old with uncomplicated *P. falciparum* malaria was tested in five African countries (Burkina Faso, Kenya, Mozambique, Uganda and Zambia). Patients were randomised (2:1) to receive either DHA-PQP or AL. Non-inferiority was assessed using a margin of -5% for the lower limit of the one-sided 97.5% confidence interval on the treatment difference (DHA-PQP vs. AL) of the day 28 polymerase chain reaction (PCR) corrected cure rate. Efficacy analysis was performed in several populations, and two of them are presented here: intention-to-treat (ITT) and enlarged per-protocol (ePP). **1553 children were randomised, 1039 receiving DHA-PQP and 514 AL. The PCR-corrected day 28 cure rate was 90.4% (ITT) and 94.7% (ePP) in the DHA-PQP group, and 90.0% (ITT) and 95.3% (ePP) in the AL group.** The lower limits of the one-sided 97.5% CI of the difference between the two treatments were -2.80% and -2.96%, in the ITT and ePP populations, respectively. In the ITT population, the Kaplan-Meier estimate of **the proportion of new infections up to Day 42 was 13.55% (95% CI: 11.35%-15.76%) for DHA-PQP vs 24.00% (95% CI: 20.11%-27.88%) for AL (p<0.0001).** **CONCLUSIONS/SIGNIFICANCE: DHA-PQP is as efficacious as AL in treating uncomplicated malaria in African children from different endemicity settings, and shows a comparable safety profile. The occurrence of new infections within the 42-day follow up was significantly lower in the DHA-PQP group, indicating a longer post-treatment prophylactic effect.**

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Clin Infect Dis. 2009 Dec 1;49(11):1629-37.

Artemether-lumefantrine versus dihydroartemisinin-piperaquine for falciparum malaria: a longitudinal, randomized trial in young Ugandan children.

Arinaitwe E, Sandison TG, Wanzira H, Kakuru A, Homsy J, Kalamya J, Kanya MR, Vora N, Greenhouse B, Rosenthal PJ, Tappero J, Dorsey G.

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Abstract

BACKGROUND: Artemisinin-based combination therapies are now widely recommended as first-line treatment for uncomplicated malaria. However, which therapies are optimal is a matter of debate. We aimed to compare the short- and longer-term efficacy of 2 leading therapies in a cohort of young Ugandan children. **METHODS:** A total of 351 children aged 6 weeks to 12 months were enrolled and followed up for up to 1 year. **Children who were at least 4 months of age, weighted at least 5 kg, and had been diagnosed as having their first episode of uncomplicated malaria were randomized to receive artemether-lumefantrine or dihydroartemisinin-piperaquine.** The same treatment was given for all subsequent episodes of uncomplicated malaria. Recrudescence and new infections were distinguished by polymerase chain reaction genotyping. Outcomes included the risk of recurrent malaria after individual treatments and the incidence of malaria treatments for individual children after randomization. **RESULTS:** A total of 113 children were randomized to artemether-lumefantrine and 119 to dihydroartemisinin-piperaquine, resulting in 320 and 351 treatments for uncomplicated falciparum malaria, respectively. **Artemether-lumefantrine was associated with a higher risk of recurrent malaria after 28 days (35% vs 11%; P = .001).** When the duration of follow-up was extended, differences in the risk of recurrent malaria decreased such that the overall incidence of malaria treatments was similar for children randomized to artemether-lumefantrine, compared with those randomized to dihydroartemisinin-piperaquine (4.82 vs 4.61 treatments per person-year; P = .63). The risk of recurrent malaria due to recrudescence parasites was similarly low in both treatment arms. **CONCLUSIONS:** Artemether-lumefantrine and dihydroartemisinin-piperaquine were both efficacious and had similar long-term effects on the risk of recurrent malaria.

PLoS One. 2009 Sep 28;4(9):e7164.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007164>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2747010/?tool=pubmed>

Randomized trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children.

Cisse B, Cairns M, Faye E, NDiaye O, Faye B, Cames C, Cheng Y, NDiaye M, Lô AC, Simondon K, Trape JF, Faye O, NDiaye JL, Gaye O, Greenwood B, Milligan P.

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Abstract

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BACKGROUND: The long terminal half life of piperazine makes it suitable for intermittent preventive treatment for malaria but no studies of its use for prevention have been done in Africa. We did a cluster randomized trial to determine whether piperazine in combination with either dihydroartemisinin (DHA) or sulfadoxine-pyrimethamine (SP) is as effective, and better tolerated, than SP plus amodiaquine (AQ), when used for intermittent preventive treatment in children delivered by community health workers in a rural area of Senegal. **METHODS:** Treatments were delivered to children 3-59 months of age in their homes once per month during the transmission season by community health workers. 33 health workers, each covering about 60 children, were randomized to deliver either SP+AQ, DHA+PQ or SP+PQ. Primary endpoints were the incidence of attacks of clinical malaria, and the incidence of adverse events. **RESULTS:** 1893 children were enrolled. Coverage of monthly rounds and compliance with daily doses was similar in all groups; 90% of children received at least 2 monthly doses. Piperazine combinations were better tolerated than SP+AQ with a significantly lower risk of common, mild adverse events. 103 episodes of clinical malaria were recorded during the course of the trial. 68 children had malaria with parasitaemia >3000/microL, 29/671 (4.3%) in the SP+AQ group, compared with 22/604 (3.6%) in the DHA+PQ group (risk difference 0.47%, 95%CI -2.3%,+3.3%), and 17/618 (2.8%) in the SP+PQ group (risk difference 1.2%, 95%CI -1.3%,+3.6%). Prevalences of parasitaemia and the proportion of children carrying Pfdhfr and Pfdhps mutations associated with resistance to SP were very low in all groups at the end of the transmission season. **CONCLUSIONS:** Seasonal IPT with SP+PQ in children is highly effective and well tolerated; the combination of two long-acting drugs is likely to impede the emergence of resistant parasites.

Malar J. 2009 Nov 30;8:272.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2789094/?tool=pubmed>

Safety and tolerability of artemether-lumefantrine versus dihydroartemisinin-piperazine for malaria in young HIV-infected and uninfected children.

Katrak S, Gasasira A, Arinaitwe E, Kakuru A, Wanzira H, Bigira V, Sandison TG, Homsy J, Tappero JW, Kamyra MR, Dorsey G.

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Abstract

BACKGROUND: Artemisinin combination therapy has become the standard of care for uncomplicated malaria in most of Africa. However, there is limited data on the safety and tolerability of these drugs, especially in young children and patients co-infected with HIV. **METHODS:** A longitudinal, randomized controlled trial was conducted in a cohort of HIV-infected and uninfected children aged 4-22 months in Tororo, Uganda. Participants were randomized to treatment with artemether-lumefantrine (AL) or dihydroartemisinin-piperazine (DP) upon diagnosis of their first episode of uncomplicated malaria and received the same regimen for all subsequent episodes. Participants were actively monitored for adverse events for 28 days and then passively for up to 63 days after treatment. This study was registered in ClinicalTrials.gov (registration # NCT00527800). **RESULTS:** A total of 122 children were

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randomized to AL and 124 to DP, resulting in 412 and 425 treatments, respectively. Most adverse events were rare, with only cough, diarrhoea, vomiting, and anaemia occurring in more than 1% of treatments. There were no differences in the risk of these events between treatment groups. Younger age was associated with an increased risk of diarrhoea in both the AL and DP treatment arms. Retreatment for malaria within 17-28 days was associated with an increased risk of vomiting in the DP treatment arm (HR = 6.47, 95% CI 2.31-18.1, $p < 0.001$). There was no increase in the risk of diarrhoea or vomiting for children who were HIV-infected or on concomitant therapy with antiretrovirals or trimethoprim-sulphamethoxazole prophylaxis. **CONCLUSION: Both AL and DP were safe and well tolerated for the treatment of uncomplicated malaria in young HIV-infected and uninfected children.** TRIAL REGISTRATION: ClinicalTrials.gov: NCT00527800; <http://clinicaltrials.gov/ct2/show/NCT00527800>.

Studies testing Amodiaquine and Artesunate combinations

Comment

Studies this year suggested that artesunate-amodiaquine (AS-AQ) is effective treatment for uncomplicated malaria in children in most African countries. Studies also confirmed that AQ-SP (sulphadoxine-pyrimethamine) and AQ alone are ineffective and that development of amodiaquine resistance may mean that AQ-containing regimens (including AS-AQ) may rapidly lose efficacy in Africa.

Malar J. 2009 Aug 23;8:203.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2745424/?tool=pubmed>

Efficacy of artesunate-amodiaquine for treating uncomplicated falciparum malaria in sub-Saharan Africa: a multi-centre analysis.

Zwang J, Olliaro P, Barennes H, Bonnet M, Brasseur P, Bukirwa H, Cohuet S, D'Alessandro U, Djimdé A, Karema C, Guthmann JP, Hamour S, Ndiaye JL, Mårtensson A, Rwagacondo C, Sagara I, Same-Ekobo A, Sirima SB, van den Broek I, Yeka A, Taylor WR, Dorsey G, Randrianarivelojosia M.

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Abstract

BACKGROUND: Artesunate and amodiaquine (AS&AQ) is at present the world's second most widely used artemisinin-based combination therapy (ACT). It was necessary to evaluate the efficacy of ACT, recently adopted by the World Health Organization (WHO) and deployed over 80 countries, in order to make an evidence-based drug policy. **METHODS:** An individual patient data (IPD) analysis was conducted on efficacy outcomes in 26 clinical studies in sub-Saharan Africa using the WHO protocol with similar primary and secondary endpoints.

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RESULTS: A total of 11,700 patients (75% under 5 years old), from 33 different sites in 16 countries were followed for 28 days. Loss to follow-up was 4.9% (575/11,700). AS&AQ was given to 5,897 patients. Of these, 82% (4,826/5,897) were included in randomized comparative trials with polymerase chain reaction (PCR) genotyping results and compared to 5,413 patients (half receiving an ACT). AS&AQ and other ACT comparators resulted in rapid clearance of fever and parasitaemia, superior to non-ACT. Using survival analysis on a modified intent-to-treat population, the Day 28 PCR-adjusted efficacy of AS&AQ was greater than 90% (the WHO cut-off) in 11/16 countries. In randomized comparative trials (n = 22), the crude efficacy of AS&AQ was 75.9% (95% CI 74.6-77.1) and the PCR-adjusted efficacy was 93.9% (95% CI 93.2-94.5). **The risk (weighted by site) of failure PCR-adjusted of AS&AQ was significantly inferior to non-ACT, superior to dihydroartemisinin-piperazine (DP, in one Ugandan site), and not different from AS+SP or AL (artemether-lumefantrine).** The risk of gametocyte appearance and the carriage rate of AS&AQ was only greater in one Ugandan site compared to AL and DP, and lower compared to non-ACT (p = 0.001, for all comparisons). Anaemia recovery was not different than comparator groups, except in one site in Rwanda where the patients in the DP group had a slower recovery.

CONCLUSION: **AS&AQ compares well to other treatments and meets the WHO efficacy criteria for use against falciparum malaria in many, but not all, the sub-Saharan African countries where it was studied.** Efficacy varies between and within countries. An IPD analysis can inform general and local treatment policies. Ongoing monitoring evaluation is required.

Malar J. 2009 Aug 20;8:200.

Population pharmacokinetics of artesunate and amodiaquine in African children.

Stepniewska K, Taylor W, Sirima SB, Ouedraogo EB, Ouedraogo A, Gansané A, Simpson JA, Morgan CC, White NJ, Kiechel JR.

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Abstract

BACKGROUND: Pharmacokinetic (PK) data on amodiaquine (AQ) and artesunate (AS) are limited in children, an important risk group for malaria. The aim of this study was to evaluate the PK properties of a newly developed and registered fixed dose combination (FDC) of artesunate and amodiaquine. **METHODS:** A prospective population pharmacokinetic study of AS and AQ was conducted in children aged six months to five years. Participants were randomized to receive the new artesunate and amodiaquine FDC or the same drugs given in separate tablets. Children were divided into two groups of 70 (35 in each treatment arm) to evaluate the pharmacokinetic properties of AS and AQ, respectively. Population pharmacokinetic models for dihydroartemisinin (DHA) and desethylamodiaquine (DeAq), the principal pharmacologically active metabolites of AS and AQ, respectively, and total artemisinin anti-malarial activity, defined as the sum of the molar equivalent plasma concentrations of DHA and artesunate, were constructed using the non-linear mixed effects approach. Relative bioavailability between products was compared by estimating the ratios (and 95% CI) between the areas under the plasma concentration-time curves (AUC). **RESULTS:** The

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two regimens had similar PK properties in young children with acute malaria. The ratio of loose formulation to fixed co-formulation AUCs, was estimated as 1.043 (95% CI: 0.956 to 1.138) for DeAq. For DHA and total anti-malarial activity AUCs were estimated to be the same.

Artesunate was rapidly absorbed, hydrolysed to DHA, and eliminated. Plasma concentrations were significantly higher following the first dose, when patients were acutely ill, than after subsequent doses when patients were usually afebrile and clinically improved. Amodiaquine was converted rapidly to DeAq, which was then eliminated with an estimated median (range) elimination half-life of 9 (7 to 12) days. **Efficacy was similar in the two treatments groups, with cure rates of 0.946 (95% CI: 0.840-0.982) in the AS+AQ group and 0.892 (95% CI: 0.787 - 0.947) in the AS/AQ group.** Four out of five patients with PCR confirmed recrudescences received AQ doses < 10 mg/kg. Both regimens were well tolerated. No child developed severe, post treatment neutropaenia (<1,000/ μ L). There was no evidence of AQ dose related hepatotoxicity, but one patient developed an asymptomatic rise in liver enzymes that was resolving by Day-28. **CONCLUSION:** The bioavailability of the co-formulated AS-AQ FDC was similar to that of the separate tablets for desethylamodiaquine, DHA and the total anti-malarial activity. **These data support the use this new AS-AQ FDC in children with acute uncomplicated falciparum malaria.**

Malar J. 2010 Jan 27;9:34.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831903/?tool=pubmed>

Efficacy of amodiaquine, sulphadoxine-pyrimethamine and their combination for the treatment of uncomplicated Plasmodium falciparum malaria in children in Cameroon at the time of policy change to artemisinin-based combination therapy.

Mbacham WF, Evehe MS, Netongo PM, Ateh IA, Mimche PN, Ajua A, Nji AM, Irene D, Echouffo-Tcheugui JB, Tawe B, Hallett R, Roper C, Targett G, Greenwood B.

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Abstract

BACKGROUND: The efficacy of amodiaquine (AQ), sulphadoxine-pyrimethamine (SP) and the combination of SP+AQ in the treatment of Cameroonian children with clinical malaria was investigated. The prevalence of molecular markers for resistance to these drugs was studied to set the baseline for surveillance of their evolution with time. **METHODS:** Seven hundred and sixty children aged 6-59 months with uncomplicated falciparum malaria were studied in three ecologically different regions of Cameroon - Mutengene (littoral equatorial forest), Yaoundé (forest-savannah mosaic) and Garoua (guinea-savannah). **Study children were randomized to receive either AQ, SP or the combination AQ+SP.** Clinical outcome was classified according to WHO criteria, as either early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) or adequate clinical and parasitological response (ACPR). The occurrence of mutations in *pfprt*, *pfmdr1*, *dhfr* and *dhps* genes was studied by either RFLP or dot blot techniques and the prevalence of these mutations related to parasitological and

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therapeutic failures. RESULTS: After correction for the occurrence of re-infection by PCR, ACPRs on day 28 for AQ, SP and AQ+SP were 71.2%, 70.1% and 80.9%, in Garoua, 79.2%, 62.5%, and 81.9% in Mutengene, and 80.3%, 67.5% and 76.2% in Yaoundé respectively. High levels of Pfcrt 76T (87.11%) and Pfmdr1 86Y mutations (73.83%) were associated with quinoline resistance in the south compared to the north, 31.67% (76T) and 22.08% (86Y). There was a significant variation ($p < 0.001$) of the prevalence of the SGK haplotype between Garoua in the north (8.33%), Yaoundé (36.29%) in the savannah-forest mosaic and Mutengene (66.41%) in the South of Cameroon and a weak relation between SGK haplotype and SP failure. The 540E mutation on the dhps gene was extremely rare (0.3%) and occurred only in Mutengene while the pfmdr1 1034K and 1040D mutations were not detected in any of the three sites. CONCLUSION: In this study the prevalence of molecular markers for quinoline and anti-folate resistances showed high levels and differed between the south and north of Cameroon. **AQ, SP and AQ+SP treatments were well tolerated but with low levels of efficacy that suggested alternative treatments were needed in Cameroon since 2005.**

J Infect Dis. 2009 Dec 1;200(11):1650-7.

<http://www.journals.uchicago.edu/doi/pdf/10.1086/647988>

Selection of parasites with diminished drug susceptibility by amodiaquine-containing antimalarial regimens in Uganda.

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Abstract

BACKGROUND: Amodiaquine (AQ) is paired with artesunate (AS) or sulfadoxine-pyrimethamine (SP) in recommended antimalarial regimens. It is unclear how readily AQ resistance will be selected with combination chemotherapy. METHODS: We collected 61 Plasmodium falciparum samples from a cohort of Ugandan children randomized for treatment with AQ-SP, AS-AQ, or artemether-lumefantrine (AL) for uncomplicated malaria. In vitro susceptibility to monodesethylamodiaquine (MDAQ) was measured with a histidine-rich protein 2-based enzyme-linked immunosorbent assay, and potential resistance-mediating polymorphisms in pfmdr1 were evaluated. RESULTS: Parasites collected from patients treated with AQ-SP or AS-AQ within the prior 12 weeks were less susceptible to MDAQ ($n = 18$; mean of the median inhibitory concentration [IC(50)], 62.9 nmol/L; range, 12.7-158.3 nmol/L) than were parasites from those not treated within 12 weeks ($n = 43$; mean IC(50), 37.5 nmol/L; range, 6.3-184.7 nmol/L; $P = .009$) or only from those patients in the treatment arm that did not receive AQ ($n = 12$; mean IC(50), 28.8 nmol/L; range, 6.3-121.8 nmol/L; $P = .004$). The proportion of strains with polymorphisms expected to mediate diminished response to AQ (pfmdr1 86Y and 1246Y) increased after AQ therapy, although differences were not statistically significant. CONCLUSIONS: **Prior therapy selected for diminished response to MDAQ, which suggests that AQ-containing regimens may rapidly lose efficacy in Africa.** The mechanism of diminished MDAQ response is not fully explained by known mutations in pfmdr1.

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J Infect Dev Ctries. 2010 Mar 8;4(2):61-9.

<http://www.jidc.org/index.php/journal/article/view/20212335>

The effect of point mutations in dihydrofolate reductase genes and multidrug resistance gene 1-86 on treatment of falciparum malaria in Sudan.

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Abstract

BACKGROUND: One of the major problems to the treatment of malaria is the emergence and spread of parasite resistant to antimalarial drugs. Due to increased chloroquine (CQ) resistance, the antifolate combinations are becoming important in the chemotherapy of falciparum malaria. However, resistance to antifolate exists and they are still effective in the above combinations. This study aimed at determining the prevalence of antimalarial drug resistance markers in *P. falciparum* isolates, involving the detection of mutations at the *mdr* 1- 86 which associates with amodiaquine resistance, and *dhfr* mutations associated with SP resistances. **METHODS:** The dot-blot/ probe hybridization, which is more sensitive and specific; it detects parasitaemia of less than 100 parasites/microl of blood, and can identify a minority parasite genotype down to 1% in a mixture, was adopted to determine multi-drug resistance (*mdr*1-86) to show the correlation of Amodiaquine (AQ) resistance and PCR/ RFLP adopted to determine dihydrofolate reductase (*dhfr*) baseline resistance to Sulphadoxine- Pyrimethamine (SP) resistance in Nubian region of southern Sudan. **A randomized open label trial of Artesunate (AS) + SP and AS+ SP was carried out in children less than 5 years.** Molecular analysis of filter paper preserved blood samples collected was carried out to provide a baseline estimate of allele prevalences. **RESULTS:** Baseline of the allele prevalence of the *mdr*1 86 locus in the AS+ AQ was successful for 80 isolates: 71(8.11%) carried parasites harbouring the *mdr*1-86 Tyr resistance allele, while 7 (89.19%) carried *mdr*1-86 Asn sensitivity allele and 2 (2.7%) were of mixed infection, having both resistance and wild type allele. Overall, the prevalence of the *dhfr* point mutation, codon 51, 59 and 108: 82.5% (132/160) carried mutations at *dhfr* (N51I, C59R or S108N), but triple mutants were rare (3.1%) in the AS + SP arm. **CONCLUSION:** The research provides the evidence that mutations present in *dhfr* and *mdr*1 86 has a significant effect on the type of treatment following SP and AQ chemotherapy. SP resistance may spread rapidly, and AS + AQ is likely to be a better option, provided AQ use is restricted to the combination. The significance of the study shows that definitely combination of drugs improves SP therapy at the study site.

Studies testing Mefloquine combinations

Am J Trop Med Hyg. 2009 Dec;81(6):979-86.

Therapeutic efficacy and effects of artesunate-mefloquine and mefloquine alone on malaria-associated anemia in children with uncomplicated *Plasmodium falciparum* malaria in southwest Nigeria.

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Abstract

The treatment efficacy and effects of artesunate-mefloquine (AMQ) and mefloquine (MQ) on malaria-associated anemia (MAA) were evaluated in 342 children \leq 10 years of age with uncomplicated *Plasmodium falciparum* malaria randomized to receive either drug/drug combination. All children recovered clinically. Fever clearance times were similar. Parasite clearance was significantly faster with AMQ (mean \pm SD = 1.4 \pm 0.6 days, 95% confidence interval [CI] = 1.3-1.5, $P < 0.0001$), but polymerase chain reaction-corrected cure rates were similar (97% versus 94%). Gametocyte carriage rates and the drug-attributable fall in hematocrit were significantly lower with AMQ (mean \pm SD = 4.8 \pm 3.8%, 95% CI = 3.6-6.0, $P = 0.03$), but the rates of resolution of MAA were similar. Both regimens were well tolerated. AMQ clears parasitemia and reduces gametocyte carriage more rapidly and causes lesser fall in hematocrit than MQ, but both regimens are effective treatment of uncomplicated *P. falciparum* malaria in Nigerian children.

Malar J. 2009 Sep 2;8:207.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2743706/?tool=pubmed>

The neurological assessment in young children treated with artesunate monotherapy or artesunate-mefloquine combination therapy for uncomplicated *Plasmodium falciparum* malaria.

Ambler MT, Dubowitz LM, Arunjeraja R, Hla EP, Thwai KL, Viladpainguen J, Singhasivanon P, Luxemburger C, Nosten F, McGready R.

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Abstract

BACKGROUND: Mefloquine and artesunate combination therapy is the recommended first-line treatment for uncomplicated malaria throughout much of south-east Asia. Concerns have been raised about the potential central nervous system (CNS) effects of both drug components and there are no detailed reports in very young children. **METHODS:** Children, aged between three months and five years, with acute uncomplicated *Plasmodium falciparum* malaria were randomized to either 7 days of artesunate monotherapy or the same schedule of artesunate plus mefloquine on day 7 and 8. Neurological testing targeting coordination and behaviour was carried out at day 0, 7, 9, 10, 14 and 28. Non-febrile healthy control children from the same population were tested on days 0, 7, 14 and 28. **RESULTS:** From December 1994 to July 1997, 91 children with uncomplicated *P. falciparum*, 45 treated with artesunate monotherapy, 46 treated with mefloquine and artesunate combination therapy and 36 non-febrile controls, underwent neurological testing. Malaria and fever had a significant negative impact on testing

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performance. By contrast, the anti-malarial treatments were not associated with worsening performances in the various components of the test. Artesunate and mefloquine do not appear to have a significant influence on coordination and behaviour. Children treated with mefloquine were significantly less likely to suffer recurrent malaria infection during follow-up compared to those treated with artesunate alone ($P = 0.033$). **CONCLUSION: In keeping with the results of randomized controlled trials in adults, mefloquine was not associated with a decrease in specific items of neurological performance. Likewise, children treated with artesunate did not perform significantly differently to control children. This study does not exclude subtle or rare treatment CNS effects of artesunate or mefloquine. Treatment of acute uncomplicated malaria results in a significant improvement on items of neurological performance.**

Comment

Two studies this year highlight the neurological impairment associated with malaria (see also section on Development: J Dev Behav Pediatr. 2009 Aug;30(4):310-8.). This study above is reassuring that mefloquine had no significant adverse effect on neurological function.

Am J Trop Med Hyg. 2010 Jan;82(1):140-4.

A randomized trial of artesunate mefloquine versus artemether lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Senegalese children.

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Abstract

An open randomized clinical trial study was carried out to compare efficacy and tolerability of artesunate mefloquine 25 mg/kg body weight (Artequin paediatric) versus artemether lumefantrine (Coartem) in the treatment of uncomplicated Plasmodium falciparum malaria in children. In each arm, 160 patients were assigned to receive either AS + MQ or AL with 28 days follow-up. The adequate clinical and **parasitological response at Day 28 for per protocol analysis was after polymerase chain reaction correction, 100% for AS + MQ and 96.8% for AL.** In the intention-to-treat analysis, the respective cure rates were 96.2% for AS + MQ and 93.7% for AL. No serious adverse events (AEs) were reported. The most frequent AE was vomiting, 30% in AS + MQ arm and 36% in AL arm. No biological significant abnormal values related to the study drug have been reported. The new pediatric artesunate mefloquine formulated in granule fixed dose combination is well adapted to children in Africa.

Studies testing Chlorproguanil-dapsone combinations

Three trials this year highlighted the dangers of chlorproguanil-dapsone combinations in settings where G6PD-deficiency is common (the above two and one from Tanzania on IPTi), with high rates of haemolysis seen in recipients. This drug was developed as a low cost treatment to address sulphadoxine-pyrimethamine resistant infections in Africa, and has now been withdrawn.

PLoS One. 2009 Aug 19;4(8):e6682.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724683/?tool=pubmed>

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0006682>

Chlorproguanil-dapsone-artesunate versus artemether-lumefantrine: a randomized, double-blind phase III trial in African children and adolescents with uncomplicated Plasmodium falciparum malaria.

Premji Z, Umeh RE, Owusu-Agyei S, Esamai F, Ezedinachi EU, Oguche S, Borrmann S, Sowunmi A, Duparc S, Kirby PL, Pamba A, Kellam L, Guiguemdé R, Greenwood B, Ward SA, Winstanley PA.

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Abstract

BACKGROUND: Chlorproguanil-dapsone-artesunate (CDA) was developed as an affordable, simple, fixed-dose artemisinin-based combination therapy for use in Africa. This trial was a randomized parallel-group, double-blind, double-dummy study to compare CDA and artemether-lumefantrine (AL) efficacy in uncomplicated Plasmodium falciparum malaria and further define the CDA safety profile, particularly its hematological safety in glucose-6-phosphate dehydrogenase (G6PD) -deficient patients. **METHODS AND FINDINGS:** The trial was conducted at medical centers at 11 sites in five African countries between June 2006 and August 2007. **1372 patients (> or =1 to <15 years old, median age 3 years) with acute uncomplicated P. falciparum malaria were randomized (2:1) to receive CDA 2/2.5/4 mg/kg once daily for three days (N = 914) or six-doses of AL over three days (N = 458).** Non-inferiority of CDA versus AL for efficacy was evaluated in the Day 28 per-protocol (PP) population using parasitological cure (polymerase chain reaction [PCR]-corrected). Cure rates were 94.1% (703/747) for CDA and 97.4% (369/379) for AL (treatment difference -3.3%, 95%CI -5.6, -0.9). CDA was non-inferior to AL, but there was simultaneous superiority of AL (upper 95%CI limit <0). **Adequate clinical and parasitological response at Day 28 (uncorrected for reinfection) was 79% (604/765) with CDA and 83% (315/381) with AL.** In patients with a G6PD-deficient genotype (94/603 [16%] hemizygous males, 22/598 [4%] homozygous females), **CDA had the propensity to cause severe and clinically concerning hemoglobin decreases: the mean hemoglobin nadir was 75 g/L (95%CI 71, 79) at Day 7 versus 97 g/L (95%CI 91, 102) for AL.** There were three deaths, unrelated to study medication (two with CDA, one with AL). **CONCLUSIONS:** Although parasitologically effective at Day 28, **the hemolytic potential of CDA in G6PD-deficient patients makes it unsuitable for use in a public health setting in Africa.** TRIAL REGISTRATION: ClinicalTrials.Gov NCT00344006.

Am J Trop Med Hyg. 2009 Dec;81(6):969-78.

Chlorproguanil-dapsone-artesunate versus chlorproguanil-dapsone: a randomized, double-blind, phase III trial in African children, adolescents, and adults with uncomplicated Plasmodium falciparum malaria.

Tiono AB, Dicko A, Ndububa DA, Agbenyega T, Pitmang S, Awobusuyi J, Pamba A, Duparc S, Goh LE, Harrell E, Carter N, Ward SA, Greenwood B, Winstanley PA.

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Abstract

This multi-center, randomized, parallel-group, double-blind, double-dummy study compared the efficacy and safety of chlorproguanil-dapsone-artesunate (CDA) and chlorproguanil-dapsone (CPG-DDS) in the treatment of falciparum malaria in Africa (Burkina Faso, Ghana, Mali, Nigeria). Six hundred patients (≥ 1 year of age) received CDA 2.0/2.5/4.0 mg/kg, and 292 CPG-DDS 2.0/2.5 mg/kg, once daily for 3 days. Day 28 parasitologic cure rate (polymerase chain reaction [PCR]-corrected, per-protocol population) was 89.1% (416/467) for CDA, non-inferior but also superior to CPG-DDS, 83.0% (176/212) (treatment difference 6.1%; 95% confidence interval [CI] 0.3, 11.9). Glucose-6-phosphate dehydrogenase (G6PD) genotype was available for 844/892 (95%) patients. Occurrences of a composite hemoglobin safety endpoint (hemoglobin drop ≥ 40 g/L or $\geq 40\%$ versus baseline, hemoglobin < 50 g/L, or blood transfusion) were CDA 13/44 (30%), CPG-DDS 7/24 (29%) in G6PD-deficient patients versus CDA 4/448 ($< 1\%$), CPG-DDS 6/221 (3%) in G6PD-normal patients. No deaths occurred. CDA was more efficacious than CPG-DDS. However, the hemolytic potential in G6PD-deficient patients does not support further development of CDA.

Other agents

Trans R Soc Trop Med Hyg. 2010 Jan;104(1):33-41. Epub 2009 Sep 5.

Argemone mexicana decoction versus artesunate-amodiaquine for the management of malaria in Mali: policy and public-health implications.

Graz B, Willcox ML, Diakite C, Falquet J, Dackuo F, Sidibe O, Giani S, Diallo D.

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Abstract

A classic way of delaying drug resistance is to use an alternative when possible. We tested the malaria treatment Argemone mexicana decoction (AM), a validated self-prepared traditional medicine made with one widely available plant and safe across wide dose variations. In an attempt to reflect the real situation in the home-based management of malaria in a remote Malian village, **301 patients with presumed uncomplicated malaria (median age 5 years)**

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were randomly assigned to receive AM or artesunate-amodiaquine [artemisinin combination therapy (ACT)] as first-line treatment. Both treatments were well tolerated. Over 28 days, second-line treatment was not required for 89% (95% CI 84.1-93.2) of patients on AM, versus 95% (95% CI 88.8-98.3) on ACT. Deterioration to severe malaria was 1.9% in both groups in children aged ≤ 5 years (there were no cases in patients aged > 5 years) and 0% had coma/convulsions. AM, now government-approved in Mali, could be tested as a first-line complement to standard modern drugs in high-transmission areas, in order to reduce the drug pressure for development of resistance to ACT, in the management of malaria. In view of the low rate of severe malaria and good tolerability, AM may also constitute a first-aid treatment when access to other antimalarials is delayed.

Clin Infect Dis. 2009 Oct 15;49(8):1195-201.

<http://www.journals.uchicago.edu/doi/pdf/10.1086/605635>

Azithromycin plus artesunate versus artemether-lumefantrine for treatment of uncomplicated malaria in Tanzanian children: a randomized, controlled trial.

Sykes A, Hendriksen I, Mtove G, Manda V, Mrema H, Rutta B, Mapunda E, Manjurano A, Amos B, Reyburn H, Whitty CJ.

National Institute for Medical Research and Muheza Designated District Hospital, Private Bag, Muheza.

Abstract

BACKGROUND: Acute febrile illness is the most common cause of outpatient attendance and mortality for children in Africa. Malaria and bacterial disease are difficult to differentiate with limited diagnostic facilities. Combinations of antibiotics and antimalarials are potentially attractive for treatment of the syndrome. Azithromycin plus artesunate (AT+AS) is an effective antimalarial combination for adults in Asia. **METHODS:** We performed an individually randomized, **open-label trial of AZ+AS versus artemether-lumefantrine (AL) involving children (age, 6-59 months) with uncomplicated malaria in Muheza, Tanzania.** The primary outcome was parasitological failure by day 28. Parasitological failure by day 42 and failure corrected for reinfection were major secondary outcomes. **RESULTS:** Of 2497 children screened, 261 were eligible; **129 were randomized to the AZ+AS arm, and 132 were randomized to the AL arm; 92% and 91%, respectively, underwent follow-up to 28 days.** Planned interim analysis was performed after 200 patients reached day 28 follow-up and led the Data and Safety Monitoring Board to halt further recruitment. All children had a complete initial response to treatment, but **69 (58%) of 119 children in the AZ+AS arm and 24 (20%) of 120 in the AL arm had asexual parasites at or by day 28 (adjusted odds ratio for failure with AZ+AS treatment, 6.1; 95% confidence interval, 3.3-11.4; P < .001).** When analysis was restricted to children with recrudescence, the parasitological failure rate was 32% in the AZ+AS arm and 9% in the AL arm. This difference was maintained at day 42. **CONCLUSIONS:** This trial does not support the use of AZ+AS as treatment for malaria or acute febrile illness in children in areas of Africa with high levels of existing antimalarial drug resistance.

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Niger J Clin Pract. 2009 Sep;12(3):252-7.

Potential toxicity of chlorpheniramine plus chloroquine for the treatment of childhood malaria.

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Abstract

OBJECTIVES: To compare the adverse effects of two regimens of chlorpheniramine plus chloroquine (CP+CQ) in children who live in a country where chloroquine resistant malaria is endemic. **METHODS:** **99 children with acute uncomplicated malaria were randomised into two treatment groups. Group I received high dose chlorpheniramine (6 mg +12 mg/day for 7 days in children = 5 years; 8 mg + 18 mg/day for 7 days in those >5 years) plus chloroquine 10 mg/kg daily for 3 days. Group II received a 50% higher dose of chlorpheniramine plus chloroquine 10 mg/kg daily for 3 days.** Outcome measures were vital signs, clinical response and parasite clearance on days 0-7 and day 14. **RESULTS:** Parasite clearance, fever clearance and cure rate were comparable for the two groups. Drowsiness occurred in 66.7% of high dose and 86.3% of higher dose CP+CQ subjects ($p = 0.05$). Compared to children treated with high dose, those treated with higher dose CP+CQ had significantly lower respiratory rates on day 2 ($p = 0.001$), day 6 ($p = 0.015$), and on day 14 ($p = 0.003$). **CONCLUSION:** **The higher rates of drowsiness and lower respiratory rates in children treated with higher dose CP+CQ calls for caution in the clinical application of the higher dose combination.** The higher dose has no additional benefit and may in fact be dangerous.

Treatment of severe or complicated malaria

(See also Emergency care)

Bull World Health Organ. 2009 Dec;87(12):896-904. Epub 2009 Jul 30.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2789363/?tool=pubmed>

Artemisinin derivatives versus quinine for cerebral malaria in African children: a systematic review.

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Abstract

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OBJECTIVE: To summarize the existing evidence on the efficacy of artemether and arteether, two artemisinin derivatives, versus quinine for treating cerebral malaria in children. **METHODS:** We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and the <http://clinicaltrials.gov> web site. We also checked the reference lists of existing systematic reviews and of all trials identified by the above methods. We searched exclusively for randomized controlled trials (RCTs) comparing artemether/arteether with quinine for treating cerebral malaria in children. Two independent reviewers assessed study eligibility and trial quality and extracted the data. **FINDINGS:** Nine RCTs were included in the analysis, and all were from Africa. Five had adequate allocation concealment. **Seven trials compared artemether with quinine (1220 children), and two compared arteether with quinine (194 children). No statistically significant difference was found between artemisinin derivatives and quinine in preventing mortality (relative risk, RR: 0.91; 95% confidence interval, CI: 0.73-1.14; I(2): 0%).** The quality of the evidence, as assessed by the Grade evidence profile, was moderate. The only serious adverse event was seen in a patient in the quinine group who developed fatal black water fever. **CONCLUSION:** Artemisinin derivatives are not inferior to quinine in preventing death in children with cerebral malaria.

Comment

The outcomes measured in this study included death (primary outcome), time to coma recovery, fever clearance time, parasite clearance time, neurological sequelae, and adverse events. Although not all studies reported adverse outcomes, there was no significant difference found in any major sequelae, including "persistent" hypoglycaemia (definition not provided). The complication of any hypoglycaemia was not reported. Depending on the way studies were reported and the analysis there was significantly shorter parasite clearance time and coma recovery time in the artemether group.

This study provides confidence in the ongoing use, where necessary, of quinine for severe cerebral malaria in Africa, but data from other regions are needed.

In this meta-analysis a greater proportion of children with QT prolongation on ECG was in the artemether group, which is unexpected as quinine has often been associated with this complication. Other studies this year highlight the cardiotoxic effects of some antimalarial drugs, particularly halofantrine (<http://www.malariajournal.com/content/8/1/289>) and point out that a distinction should be made between common but asymptomatic QT-interval prolongation and the much less common ventricular arrhythmias, such as torsades de pointes, which is rare but can be fatal.

Treatment of vivax malaria

Malar J. 2010 Apr 21;9:105.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2864284/?tool=pubmed>

Dihydroartemisinin-piperaquine versus chloroquine to treat vivax malaria in Afghanistan: an open randomized, non-inferiority, trial.

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Abstract

BACKGROUND: Afghanistan's national guidelines recommend chloroquine for the treatment of Plasmodium vivax infection, the parasite responsible for the majority of its malaria burden. Chloroquine resistance in P. vivax is emerging in Asia. Therapeutic responses across Afghanistan have not been evaluated in detail. **METHODS:** Between July 2007 and February 2009, an **open-label, randomized controlled trial of chloroquine and dihydroartemisinin-piperaquine in patients aged three months and over with slide-confirmed P. vivax mono-infections** was conducted. Consistent with current national guidelines, primaquine was not administered. Subjects were followed up daily during the acute phase of illness (days 0-3) and weekly until day 56. The primary endpoint was the overall cumulative parasitological failure rate at day 56 after the start of treatment, with the hypothesis being that dihydroartemisinin-piperaquine was non-inferior compared to chloroquine (Delta = 5% difference in proportion of failures). **RESULTS:** Of 2,182 individuals with positive blood films for P. vivax, 536 were enrolled in the trial. **The day 28 cure rate was 100% in both treatment groups. Parasite clearance was more rapid with dihydroartemisinin-piperaquine than chloroquine. At day 56, there were more recurrent infections in the chloroquine arm (8.9%, 95% CI 6.0-13.1%) than the dihydroartemisinin-piperaquine arm (2.8%, 95% CI 1.4-5.8%), a difference in cumulative recurrence rate of 6.1% (2-sided 90% CI +2.6 to +9.7%).** The log-rank test comparing the survival curves confirmed the superiority of dihydroartemisinin-piperaquine over chloroquine (p = 0.003). Multivariate analysis showed that a lower initial haemoglobin concentration was also independently associated with recurrence. Both regimens were well tolerated and no serious adverse events were reported. **CONCLUSIONS:** Chloroquine remains an efficacious treatment for the treatment of vivax malaria in Afghanistan. In a setting where radical therapy cannot be administered, dihydroartemisinin-piperaquine provides additional benefit in terms of post-treatment prophylaxis, reducing the incidence of recurrence from 4-8 weeks after treatment.

(See also section on dihydroartemisinin-piperaquine in treatment of uncomplicated malaria.)

Acta Trop. 2009 Nov;112(2):188-92. Epub 2009 Aug 3.

Prevention of Plasmodium vivax malaria recurrence: efficacy of the standard total dose of primaquine administered over 3 days.

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Abstract

BACKGROUND: The standard total dose (STD) of primaquine to prevent Plasmodium vivax recurrence is 0.25mg/kg day administered over 14 days (STD-14). We evaluated, in an endemic zone of Colombia, the anti-recurrence efficacy of the STD dose administered over 3 and 14 days, and of sub-STD dose administered over 3 days (71%STD-3, 50%STD-3). **METHODS:** A controlled clinical trial was carried out with 188 subjects allocated into one of four treatment groups: STD-14, STD-3, 71%STD-3, 50%STD-3. **RESULTS:** Recurrences during the 120 days

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of follow-up were 15% in STD-14, and 57% in STD-3. Treatment with 71%STD-3 and 50%STD-3 resulted in recurrence in >48% subjects within 120 days after the primary episode. High daily doses (1.17 mg/kg day) were well tolerated. **CONCLUSIONS: (a) The standard dose and regimen (STD-14) of primaquine to prevent P. vivax relapse is recommended. The administration of the same dose over 3 days (STD-3) should be avoided; (b) doses lower than the STD doses administered over 3 days are ineffective in preventing relapse.**

Acta Trop. 2010 Feb;113(2):105-13. Epub 2009 Oct 14.

Therapeutic efficacy of chloroquine and chloroquine plus primaquine for the treatment of Plasmodium vivax in Ethiopia.

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Abstract

Plasmodium vivax is the second most important cause of morbidity in Ethiopia. There is, however, little information on *P. vivax* resistance to chloroquine and chloroquine plus primaquine treatment although these drugs have been used as the first line treatment for over 50 years. We assessed the efficacy of standard chloroquine and chloroquine plus primaquine treatment for *P. vivax* infections in a randomized open-label comparative study in Debre Zeit and Nazareth in East Shoa, Ethiopia. A total of 290 patients with microscopically confirmed *P. vivax* malaria who presented to the outpatient settings of the two laboratory centers were enrolled: 145 patients were randomized to receive CQ and 145 to receive CQ+PQ treatment. Participants were followed-up for 28-157 days according to the WHO procedures. There were 12 (6.5%) lost to follow-up patients and 9 (3.1%) withdrawals. In all, 96% (277/290) of patients were analysed at day 28. Baseline characteristics were similar in all treatment groups. In all, 98.6% (275/277) of patients had cleared their parasitemia on day 3 with no difference in mean parasite clearance time between regimens (48.34+/-17.68, 50.67+/-15.70 h for the CQ and CQ+PQ group, respectively, P=0.25). **The cumulative incidence of therapeutic failure at day 28 by a life-table analysis method was 5.76% (95% CI: 2.2-14.61) and 0.75% (95% CI: 0.11-5.2%) in the CQ and CQ+PQ group, respectively (P=0.19). The relapse rate was 8% (9/108) for the CQ group and 3% (4/132) for the comparison group (P=0.07). The cumulative risk of relapse at day 157 by a life-table method was 61.8% (95% CI: 20.1-98.4%) in the CQ group, compared with 26.3% (95% CI: 7.5-29.4%) in the CQ+PQ group (P=0.0038).** The study confirms the emergence of CQ and PQ resistance/treatment failure in *P. vivax* malaria in Ethiopia. Although treatment failures were detected, they were similar between the treatment groups. We recommend regular monitoring and periodic evaluation of the efficacy of these antimalarial drugs in systematically selected sentinel sites to detect further development of resistance and to make timely national antimalarial drug policy changes.

Malnutrition

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

Lancet. 2009 Jul 11;374(9684):136-44.

Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi.

Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, Sadler K, Bahwere P, Collins S.

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Abstract

BACKGROUND: Severe acute malnutrition affects 13 million children worldwide and causes 1-2 million deaths every year. **Our aim was to assess the clinical and nutritional efficacy of a probiotic and prebiotic functional food for the treatment of severe acute malnutrition in a HIV-prevalent setting.** **METHODS:** We recruited 795 Malawian children (age range 5 to 168 months [median 22, IQR 15 to 32]) from July 12, 2006, to March 7, 2007, into a double-blind, randomised, placebo-controlled efficacy trial. For generalisability, all admissions for severe acute malnutrition treatment were eligible for recruitment. **After stabilisation with milk feeds, children were randomly assigned to ready-to-use therapeutic food either with (n=399) or without (n=396) Synbiotic2000 Forte.** Average prescribed Synbiotic dose was 10(10) colony-forming units or more of lactic acid bacteria per day for the duration of treatment (median 33 days). **Primary outcome was nutritional cure (weight-for-height >80% of National Center for Health Statistics median on two consecutive outpatient visits). Secondary outcomes included death, weight gain, time to cure, and prevalence of clinical symptoms (diarrhoea, fever, and respiratory problems).** Analysis was on an intention-to-treat basis. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN19364765. **FINDINGS: Nutritional cure was similar in both Synbiotic and control groups (53.9% [215 of 399] and 51.3% [203 of 396]; p=0.40). Secondary outcomes were also similar between groups. HIV seropositivity was associated with worse outcomes overall, but did not modify or confound the negative results.** Subgroup analyses showed possible trends towards reduced outpatient mortality in the Synbiotic group (p=0.06). **INTERPRETATION: In Malawi, Synbiotic2000 Forte did not improve severe acute malnutrition outcomes.** The observation of reduced outpatient mortality might be caused by bias, confounding, or chance, but is biologically plausible, has potential for public health impact, and should be explored in future studies.

J Med Assoc Thai. 2010 Mar;93(3):301-9.

Supplement of three eggs a week improves protein malnutrition in Thai children from rural areas.

Mayurasakorn K, Sitphahul P, Hongto PO.

Randomised trials in child health in developing countries 2009-10

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Abstract

BACKGROUND: Protein Malnutrition is one of the most important health indexes that affect children's growth and development. In Thailand National Health Survey 2004, 21.5% of primary school students living in the rural area were below the 90th percentile of the standard weight for age. **OBJECTIVE:** To compare nutritional status with serum proteins and lipids, and to determine the effect of egg supplement for primary school students aged 6-15 years.

MATERIAL AND METHOD: **A randomized experimental study was performed in 417 participants received an addition of either three or ten eggs per week for 12 consecutive weeks to basal diet.** **RESULTS:** The anthropometric and biochemical indexes were measured, 29.1% and 20.8% of whom were Protein Malnutrition according to serum albumin and PreAlbumin's criteria, respectively. Albumin and PreAlbumin levels were positively correlated with Total Cholesterol and LDL-C levels. **No difference in any biochemical index has been found between 3 eggs/wk group and 10 eggs/wk group.** Besides, due to continuing egg supplement, Total Cholesterol, LDL and ratio of Total Cholesterol to HDL level have decreased ($p < 0.001$) but albumin, PreAlbumin and HDL levels have demonstrated significantly increasing levels ($p < 0.001$). **CONCLUSION:** Nowadays in rural areas of Thailand there are still primary school students with protein malnutrition especially in rural area. **An addition of at least 3 eggs/wk supplements can effectively correct the problem of protein malnutrition among primary school students at risk as shown by biochemical indices, and it benefits the blood cholesterol level as well.**

Maternal health

Maternal micronutrients

*** Am J Epidemiol. 2009 Nov 1;170(9):1127-36. Epub 2009 Sep 24.

Antenatal and postnatal iron supplementation and childhood mortality in rural Nepal: a prospective follow-up in a randomized, controlled community trial.

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Abstract

The long-term benefits of antenatal iron supplementation in child survival are not known. In 1999-2001, **4,926 pregnant women in rural Nepal participated in a cluster-randomized, double-masked, controlled trial involving 4 alternative combinations of micronutrient supplements, each containing vitamin A.** The authors examined the impact on birth weight and early infant mortality in comparison with controls, who received vitamin A only. They followed the surviving offspring of these women at approximately age 7 years to study effects of in utero supplementation on survival. Of 4,130 livebirths, 209 infants died in the first 3 months and 8 were lost to follow-up. Of those remaining, 3,761 were followed, 150 died between ages 3

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months and 7 years, and 152 were lost to follow-up. **Mortality rates per 1,000 child-years from birth to age 7 years differed by maternal supplementation group, as follows: folic acid, 13.4; folic acid-iron, 10.3; folic acid-iron-zinc, 12.0; multiple micronutrients; 14.0; and controls, 15.2.** Hazard ratios were 0.90 (95% confidence interval (CI): 0.65, 1.22), 0.69 (95% CI: 0.49, 0.99), 0.80 (95% CI: 0.58, 1.11), and 0.93 (95% CI: 0.66, 1.31), respectively, in the 4 supplementation groups. **Maternal iron-folic acid supplementation reduced mortality among these children by 31% between birth and age 7 years.** These results provide additional motivation for strengthening antenatal iron-folic acid programs.

*** Food Nutr Bull. 2009 Jun;30(2 Suppl):S207-14.

Programmatic effects of a large-scale multiple-micronutrient supplementation trial in Indonesia: using community facilitators as intermediaries for behavior change.

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Abstract

BACKGROUND: Clinical trials can serve as an opportunity gateway for enhanced health benefits to the target population, above and beyond the specific intervention being tested. **OBJECTIVE:** **The Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT), a randomized, controlled clinical trial in Lombok, Indonesia, found that supplementation during pregnancy with multiple micronutrients reduced 90-day infant mortality by nearly 20% as compared with iron-folic acid.** This trial was designed as both a program and research trial and used community facilitators to serve as liaisons between the study and the pregnant women. This analysis documents the programmatic impacts of SUMMIT on health-seeking and early infant mortality resulting from community facilitators' field activities. **METHODS:** Data on compliance, human resource practices, health-seeking, and health outcomes from the 31,290 SUMMIT enrollees were analyzed. **RESULTS:** Overall compliance with either iron-folic acid or multiple micronutrients was high in the program, at 85.0%. Early prenatal care visits increased significantly. Sixty-three percent of primiparous women used a skilled birth attendant (SBA); among multiparous women, the rate of use of a SBA rose from 35% for the last birth to 53%. Use of a SBA resulted in a 30% reduction in early infant mortality (RR, 0.70; 95% CI, 0.59 to 0.83; $p < .0001$), independently of any reductions due to multiple micronutrients. The community facilitators played a central role in improving health-seeking; however, the quality of the community facilitators' performance was associated with the impact of the micronutrient supplement on infant health. In a subsample of community facilitators, better-performing facilitators were found to markedly improve the overall impact of the multiple micronutrients on early infant mortality (RR, 0.67; 95% CI, 0.49 to 0.92; $p = .0117$). In contrast, infants of women with poorly performing community facilitators were found to derive no additional benefit from the multiple micronutrients (RR, 1.04; 95% CI, 0.64 to 1.72; $p = .8568$). **CONCLUSIONS:** **Systematic enhancements to the quality of implementation of SUMMIT led to significant increases in use of SBAs at delivery, resulting in a 30%**

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reduction in early infant mortality independent of the impact of micronutrient supplementation. Therefore, if women were to consume multiple micronutrients on a regular basis and were to use a SBA at delivery, the risk of early infant mortality could be reduced by nearly 50%. The impacts of community facilitators in effecting changes in women's health behaviors are notable and are applicable to other health programs. Enhancements to program implementation should be driven by evidence, be accountable to the communities the program serves, and be evaluated on the basis of measurable gains in health for women and children.

J Nutr. 2010 Mar;140(3):618-24. Epub 2010 Jan 6.

Maternal multiple micronutrient supplementation has limited impact on micronutrient status of Bangladeshi infants compared with standard iron and folic acid supplementation.

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Abstract

Knowledge about the impact of maternal food and micronutrient supplementation on infant micronutrient status is limited. We examined the effect of maternal food and micronutrient supplementation on infant micronutrient status in the Maternal and Infant Nutrition Interventions in Matlab Trial. Pregnant women (n = 4436) were randomized to Early or Usual promotion of enrollment in a food supplementation program. In addition, they were randomly allocated to 1 of the following 3 types of daily micronutrient supplements provided from wk 14 of gestation to 3 mo postpartum: 1) folic acid and 30 mg iron (Fe30Fol); 2) folic acid and 60 mg iron; or 3) a multiple micronutrient including folic acid and 30 mg iron (MMS). At 6 mo, infant blood samples (n = 1066) were collected and analyzed for hemoglobin and plasma ferritin, zinc, retinol, vitamin B-12, and folate. The vitamin B-12 concentration differed between the micronutrient supplementation groups (P = 0.049). The prevalence of vitamin B-12 deficiency was lower in the MMS group (26.1%) than in the Fe30Fol group (36.5%) (P = 0.003). The prevalence of zinc deficiency was lower in the Usual food supplementation group (54.1%) than in the Early group (60.2%) (P = 0.046). There were no other differential effects according to food or micronutrient supplementation groups. We conclude that maternal multiple micronutrient supplementation may have a beneficial effect on vitamin B-12 status in infancy.

Br J Nutr. 2010 Jun;103(12):1784-91. Epub 2010 Mar 9.

Sex differences in the effects of maternal vitamin supplements on mortality and morbidity among children born to HIV-infected women in Tanzania.

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Abstract

We examined whether there are sex differences in the effect of vitamin supplements on birth outcomes, mortality and morbidity by 2 years of age among children born to HIV-infected women in Tanzania. A randomised placebo-controlled trial was conducted among 959 mother-infant pairs. **HIV-infected pregnant women were randomly assigned to receive a daily oral dose of one of four regimens: multivitamins (vitamins B-complex, C and E), vitamin A plus beta-carotene, multivitamins including vitamin A plus beta-carotene or placebo. Supplements were administered during pregnancy and continued after delivery. The beneficial effect of multivitamins on decreasing the risk of low birth weight was stronger among girls (relative risks (RR) = 0.39, 95 % CI 0.22, 0.67) than among boys (RR = 0.81, 95 % CI 0.44, 1.49; P for interaction = 0.08). Maternal multivitamin supplements resulted in 32 % reduction in mortality among girls (RR = 0.68, 95 % CI 0.47, 0.97), whereas no effect was found among boys (RR = 1.20, 95 % CI 0.80, 1.78; P for interaction = 0.04). Multivitamins had beneficial effects on the overall risks of diarrhoea that did not differ by sex. Vitamin A plus beta-carotene alone increased the risk of HIV transmission, but had no effects on mortality, and we found no sex differences in these effects. Sex differential effects of multivitamins on mortality may be due to sex-related differences in the immunological or genetic factors. More research is warranted to examine the effect of vitamins by sex and better understand biological mechanisms mediating such effects.**

Lancet. 2010 May 8;375(9726):1640-9.

Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial.

Kirkwood BR, Hurt L, Amenga-Etego S, Tawiah C, Zandoh C, Danso S, Hurt C, Edmond K, Hill Z, Ten Asbroek G, Fenty J, Owusu-Agyei S, Campbell O, Arthur P; ObaapaVitA Trial Team.

Collaborators (24)

Arthur P, Kirkwood BR, Campbell O, Bellamy R, Edmond K, Hurt L, Avan B, Gunasekera P, ten Asbroek G, Owusu-Agyei S, Zandoh C, Soremekun S, Manu A, Hill Z, Tawiah C, Adjei E, Kendall C, Amenga-Etego S, Danso S, Tomlin K, Grundy C, Stämme V, Hurt C, Fenty J.

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Abstract

BACKGROUND: A previous trial in Nepal showed that supplementation with vitamin A or its precursor (betacarotene) in women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16-63). We assessed the effect of vitamin A supplementation in women in Ghana. **METHODS:** ObaapaVitA was a cluster-randomised, double-blind, placebo-controlled trial undertaken in seven districts in Brong Ahafo Region in Ghana. The trial area was divided into 1086 small geographical clusters of compounds with fieldwork areas consisting of four

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contiguous clusters. All women of reproductive age (15-45 years) who gave informed consent and who planned to remain in the area for at least 3 months were recruited. **Participants were randomly assigned by cluster of residence to receive a vitamin A supplement (25 000 IU retinol equivalents) or placebo capsule orally once every week.** Randomisation was blocked and based on an independent, computer-generated list of numbers, with two clusters in each fieldwork area allocated to vitamin A supplementation and two to placebo. **Capsules were distributed during home visits undertaken every 4 weeks, when data were gathered on pregnancies, births, and deaths.** Primary outcomes were pregnancy-related mortality and all-cause female mortality. Cause of death was established by verbal post mortems. Analysis was by intention to treat (ITT) with random-effects regression to account for the cluster-randomised design. Adverse events were synonymous with the trial outcomes. This trial is registered with ClinicalTrials.gov, number NCT00211341. **FINDINGS:** 544 clusters (104 484 women) were randomly assigned to vitamin A supplementation and 542 clusters (103 297 women) were assigned to placebo. The main reason for participant drop out was migration out of the study area. In the ITT analysis, **there were 39 601 pregnancies and 138 pregnancy-related deaths in the vitamin A supplementation group (348 deaths per 100 000 pregnancies) compared with 39 234 pregnancies and 148 pregnancy-related deaths in the placebo group (377 per 100 000 pregnancies); adjusted odds ratio 0.92, 95% CI 0.73-1.17; p=0.51.** 1326 women died in 292 560 woman-years in the vitamin A supplementation group (453 deaths per 100 000 years) compared with 1298 deaths in 289 310 woman-years in the placebo group (449 per 100 000 years); adjusted rate ratio 1.01, 0.93-1.09; p=0.85. **INTERPRETATION:** The body of evidence, although limited, does not support inclusion of vitamin A supplementation for women in either safe motherhood or child survival strategies. **FUNDING:** UK Department for International Development, and USAID. Copyright 2010 Elsevier Ltd. All rights reserved.

Womens groups

*** Lancet. 2010 Apr 3;375(9721):1182-92. Epub 2010 Mar 6.

Effect of a participatory intervention with women's groups on birth outcomes and maternal depression in Jharkhand and Orissa, India: a cluster-randomised controlled trial.

Tripathy P, Nair N, Barnett S, Mahapatra R, Borghi J, Rath S, Rath S, Gope R, Mahto D, Sinha R, Lakshminarayana R, Patel V, Pagel C, Prost A, Costello A.

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Abstract

BACKGROUND: Community mobilisation through participatory women's groups might improve birth outcomes in poor rural communities. We therefore assessed this approach in a largely tribal and rural population in three districts in eastern India. **METHODS:** From 36 clusters in Jharkhand and Orissa, with an estimated population of 228 186, we assigned 18 clusters to intervention or control using stratified randomisation. Women were eligible to

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participate if they were aged 15-49 years, residing in the project area, and had given birth during the study. **In intervention clusters, a facilitator convened 13 groups every month to support participatory action and learning for women, and facilitated the development and implementation of strategies to address maternal and newborn health problems.** The primary outcomes were reductions in neonatal mortality rate (NMR) and maternal depression scores. Analysis was by intention to treat. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN21817853. FINDINGS: After baseline surveillance of 4692 births, we monitored outcomes for 19 030 births during 3 years (2005-08). **NMRs per 1000 were 55.6, 37.1, and 36.3 during the first, second, and third years, respectively, in intervention clusters, and 53.4, 59.6, and 64.3, respectively, in control clusters. NMR was 32% lower in intervention clusters adjusted for clustering, stratification, and baseline differences (odds ratio 0.68, 95% CI 0.59-0.78) during the 3 years, and 45% lower in years 2 and 3 (0.55, 0.46-0.66).** Although we did not note a significant effect on maternal depression overall, reduction in moderate depression was 57% in year 3 (0.43, 0.23-0.80). INTERPRETATION: This intervention could be used with or as a potential alternative to health-worker-led interventions, and presents new opportunities for policy makers to improve maternal and newborn health outcomes in poor populations. FUNDING: Health Foundation, UK Department for International Development, Wellcome Trust, and the Big Lottery Fund (UK). Copyright 2010 Elsevier Ltd. All rights reserved.

Lancet. 2010 Apr 3;375(9721):1193-202. Epub 2010 Mar 6.

Effect of scaling up women's groups on birth outcomes in three rural districts in Bangladesh: a cluster-randomised controlled trial.

Azad K, Barnett S, Banerjee B, Shaha S, Khan K, Rego AR, Barua S, Flatman D, Pagel C, Prost A, Ellis M, Costello A.

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Abstract

BACKGROUND: Two recent trials have shown that women's groups can reduce neonatal mortality in poor communities. We assessed the effectiveness of a scaled-up development programme with women's groups to address maternal and neonatal care in three rural districts of Bangladesh. **METHODS:** 18 clusters (with a mean population of 27 953 [SD 5953]) in three districts were randomly assigned to either intervention or control (nine clusters each) by use of stratified randomisation. For each district, cluster names were written on pieces of paper, which were folded and placed in a bottle. The first three cluster names drawn from the bottle were allocated to the intervention group and the remaining three to control. All clusters received health services strengthening and basic training of traditional birth attendants. **In intervention clusters, a facilitator convened 18 groups every month to support participatory action and learning for women, and to develop and implement strategies to address maternal and neonatal health problems.** Women were eligible to participate if they were aged 15-49 years, residing in the project area, and had given birth during the study period (Feb 1, 2005, to Dec 31,

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2007). Neither study investigators nor participants were masked to treatment assignment. In a population of 229 195 people (intervention clusters only), 162 women's groups provided coverage of one group per 1414 population. The primary outcome was neonatal mortality rate (NMR). Analysis was by intention to treat. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN54792066. FINDINGS: We monitored outcomes for 36 113 births (intervention clusters, n=17 514; control clusters, n=18 599) in a population of 503 163 over 3 years. **From 2005 to 2007, there were 570 neonatal deaths in the intervention clusters and 656 in the control clusters. Cluster-level mean NMR (adjusted for stratification and clustering) was 33.9 deaths per 1000 livebirths in the intervention clusters compared with 36.5 per 1000 in the control clusters (risk ratio 0.93, 95% CI 0.80-1.09).** INTERPRETATION: For participatory women's groups to have a significant effect on neonatal mortality in rural Bangladesh, detailed attention to programme design and contextual factors, enhanced population coverage, and increased enrolment of newly pregnant women might be needed. FUNDING: Women and Children First, the UK Big Lottery Fund, Saving Newborn Lives, and the UK Department for International Development. Copyright 2010 Elsevier Ltd. All rights reserved.

Antenatal care

Sex Transm Dis. 2009 Nov;36(11):714-20.

One-stop service for antenatal syphilis screening and prevention of congenital syphilis in Ulaanbaatar, Mongolia: a cluster randomized trial.

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Abstract

BACKGROUND: This cluster randomized trial was performed to test whether one-stop service could better prevent congenital syphilis than the conventional antenatal screening service in Mongolia. **METHODS:** Out of 14 antenatal clinics in 6 districts of Ulaanbaatar, 7 were randomly selected for the one-stop service and the remaining for the conventional service. Intervention clinics provided on-site rapid syphilis testing and immediate treatment for positive cases and their partners. In control clinics, syphilis screening services with routine off-site rapid plasma regain testing and case management were followed. Analysis was intention to treat. **RESULTS:** Of 3850 antenatal women recruited in each group, the proportion of syphilis testing at the first visit and third trimester was over 99% in the intervention group and 79.6% and 61.5% in the control group, respectively ($P < 0.001$ for both periods). Correspondingly, syphilis cases detected in the intervention group were 73 (1.9%) and 20 (0.5%) for the first visit and third trimester, respectively, and 27 (0.9%) and 2 (0.08%) in the control group; and 98.9% (92/93) of the detected cases in the intervention group and 89.6% (26/29) in the control group were adequately treated ($P = 0.02$). The corresponding treatment rates for sexual partners were 94.6% and 55.2% ($P < 0.001$). **One congenital syphilis case out of 3632 deliveries in the**

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intervention group, compared to 15 of 3552 in the control group, was diagnosed, a reduction of 93.5% (95% confidence interval, 66.0%-98.6%). CONCLUSIONS: One-stop services increased the detection rate of syphilis, treated more positive women and their partners, and effectively reduced the rate of congenital syphilis.

Comment

This is an important study, showing that antenatal point-of-care testing and immediate treatment for maternal syphilis can significantly reduce the number of babies born with congenital syphilis. The traditional laboratory based serological testing for syphilis delays treatment because of the need for mothers to return to antenatal clinics to receive test results before antibiotic treatment, the difficulty of obtaining laboratory tests in remote health clinics where ANC is provided. Rapid diagnostic tests and immediate treatment for maternal syphilis have the potential to reduce stillbirth and neonatal mortality rates and improve maternal health.

Perinatal care

Large-scale RCTs and meta-analyses this year show that maternal antibiotics in women undergoing caesarean section do prevent serious maternal infections, antibiotics given to HIV-infected mothers in labour to prevent chorioamnionitis don't increase the risk of neonatal mortality, and that vaginal swabbing with chlorhexidine has no effect on neonatal sepsis.

Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000933.

<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000933/frame.html>

Antibiotic prophylaxis for cesarean section.

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Abstract

BACKGROUND: The single most important risk factor for postpartum maternal infection is cesarean delivery. **OBJECTIVES:** The objective of this review was to assess the effects of prophylactic antibiotic treatment on infectious complications in women undergoing cesarean delivery. **SEARCH STRATEGY:** We searched the Cochrane Pregnancy and Childbirth Group trials register (January 2002) and the Cochrane Controlled Trials Register (The Cochrane Library, Issue 4, 2001). **SELECTION CRITERIA:** Randomized trials comparing antibiotic prophylaxis or no treatment for both elective and non-elective cesarean section. **DATA COLLECTION AND ANALYSIS:** Two reviewers assessed trial quality and extracted data. **MAIN RESULTS:** Eighty-one trials were included. **Use of prophylactic antibiotics in women undergoing cesarean section substantially reduced the incidence of episodes of fever, endometritis, wound infection, urinary tract infection and serious infection after cesarean section. The reduction in the risk of endometritis with antibiotics was similar across**

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different patient groups: the relative risk (RR) for endometritis for elective cesarean section (number of women = 2037) was 0.38 (95% confidence interval (CI) 0.22 to 0.64); the RR for non-elective cesarean section (n = 2132) was 0.39 (95% CI 0.34 to 0.46); and the RR for all patients (n = 11,937) was 0.39 (95% CI 0.31 to 0.43). Wound infections were also reduced: for elective cesarean section (n = 2015) RR 0.73 (95% CI 0.53 to 0.99); for non-elective cesarean section (n = 2780) RR 0.36 (95% CI 0.26 to 0.51); and for all patients (n = 11,142) RR 0.41 (95% CI 0.29 to 0.43). AUTHORS' CONCLUSIONS: The reduction of endometritis by two thirds to three quarters and a decrease in wound infections justifies a policy of recommending prophylactic antibiotics to women undergoing elective or non-elective cesarean section.

Lancet. 2009 Dec 5;374(9705):1909-16. Epub 2009 Oct 19.

Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial.

Cutland CL, Madhi SA, Zell ER, Kuwanda L, Laque M, Groome M, Gorwitz R, Thigpen MC, Patel R, Velaphi SC, Adrian P, Klugman K, Schuchat A, Schrag SJ; PoPS Trial Team.

Collaborators (25)

Edwards K, Cooper P, Knoll MD, McIntyre J, Temmerman M, Hofmeyr GJ, Miotti P, Pattinson R, Saloojee H, Whitney C, von Gottberg A, Buchmann E, Rubin D, Jivkov B, Moodley A, Fareed W, Fourie S, Gosai V, Hassan R, Jaques G, Jassat W, Jones S, Kohler M, Lakha P, Marran K.

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Abstract

BACKGROUND: About 500,000 sepsis-related deaths per year arise in the first 3 days of life. On the basis of results from non-randomised studies, use of vaginal chlorhexidine wipes during labour has been proposed as an intervention for the prevention of early-onset neonatal sepsis in developing countries. We therefore assessed the efficacy of chlorhexidine in early-onset neonatal sepsis and vertical transmission of group B streptococcus. **METHODS:** In a trial in Soweto, South Africa, **8011 women (aged 12-51 years) were randomly assigned in a 1:1 ratio to chlorhexidine vaginal wipes or external genitalia water wipes during active labour, and their 8129 newborn babies were assigned to full-body (intervention group) or foot (control group) washes with chlorhexidine at birth, respectively.** In a subset of mothers (n=5144), we gathered maternal lower vaginal swabs and neonatal skin swabs after delivery to assess colonisation with potentially pathogenic bacteria. Primary outcomes were neonatal sepsis in the first 3 days of life and vertical transmission of group B streptococcus. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00136370. **FINDINGS: Rates of neonatal sepsis did not differ between the groups (chlorhexidine 141 [3%] of 4072 vs control 148 [4%] of 4057; p=0.6518).** Rates of colonisation with group B streptococcus in newborn babies born to mothers in the chlorhexidine (217 [54%] of 401) and control groups (234 [55%] of 429) did not differ (efficacy -0.05%, 95% CI -9.5 to 7.9).

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INTERPRETATION: Because chlorhexidine intravaginal and neonatal wipes did not prevent neonatal sepsis or the vertical acquisition of potentially pathogenic bacteria among neonates, we need other interventions to reduce childhood mortality.

Pediatrics. 2009 Jul;124(1):e137-44.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2764263/?tool=pubmed>

Intrapartum antibiotic exposure and early neonatal, morbidity, and mortality in Africa.

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Abstract

BACKGROUND: Infants born to women who receive intrapartum antibiotics may have higher rates of infectious morbidity and mortality than unexposed infants. **OBJECTIVE:** Our goal was to determine the association of maternal intrapartum antibiotics and early neonatal morbidity and mortality. **METHODS:** We performed secondary analysis of data from a multisite randomized, placebo-controlled clinical trial of antibiotics to prevent chorioamnionitis-associated mother-to-child transmission of HIV-1 and preterm birth in sub-Saharan Africa. Early neonatal morbidity and mortality were analyzed. In an intention-to-treat (ITT) analysis, infants born to women randomly assigned to antibiotics or placebo were compared. In addition, non-ITT analysis was performed because some women received nonstudy antibiotics for various clinical indications. **RESULTS:** Overall, 2659 pregnant women were randomly assigned. Of these, 2466 HIV-1-infected and HIV-1-uninfected women delivered 2413 live born and 84 stillborn infants. **In the ITT analysis, there were no significant associations between exposure to antibiotics and early neonatal outcomes. Non-ITT analyses showed more illness at birth (11.2% vs 8.6%, P = .03) and more admissions to the special care infant unit (12.6% vs 9.8%, P = .04) among infants exposed to maternal intrapartum antibiotics than among unexposed infants.** Additional analyses revealed greater early neonatal morbidity and mortality among infants of mothers who received nonstudy antibiotics than of mothers who received study antibiotics. **CONCLUSIONS: There is no association between intrapartum exposure to antibiotics and early neonatal morbidity or mortality.** The associations observed in non-ITT analyses are most likely the result of women with peripartum illnesses being more likely to receive nonstudy antibiotics.

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2010 May;6(3):377-81.

Comparison between massage and music therapies to relieve the severity of labor pain.

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Abstract

BACKGROUND: During labor, women experience a high level of intense, stressful and steady pain that may negatively affect both mothers and neonates. Painkillers have previously been used for childbearing women, but nowadays, owing to some well-known limitations and serious side effects, nonpharmacologic methods such as massage and music therapies are being broadly recommended. The present clinical trial was conducted to compare the effects of massage and music therapies on the severity of labor pain in the Ilam province of western Iran. **MATERIALS & METHODS:** Overall, **101 primigravidae who were hospitalized for vaginal delivery were recruited and randomly stratified into two groups of either massage (n = 51) or music (n = 50) therapies.** Pain was measured using the visual analog scale and the two groups were compared in terms of pain severity before and after the interventions. **RESULTS: Mothers in the massage therapy group had a lower level of pain compared with those in the music therapy group (p = 0.009).** A significant difference was observed between the two groups in terms of pain severity after intervention (p = 0.01). Agonizing, or most severe, labor pain was significantly relieved after massage therapy (p = 0.001). **CONCLUSION: Massage therapy was an effective method for reducing and relieving labor pain compared with music therapy and can be clinically recommended as an alternative, safe and affordable method of pain relief** where using either pharmacological or nonpharmacological methods are optional.

Neonatal care

*** Int J Epidemiol. 2010 Apr;39 Suppl 1:i144-54.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2845870/pdf/dyq031.pdf>

'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications.

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Abstract

BACKGROUND: 'Kangaroo mother care' (KMC) includes thermal care through continuous skin-to-skin contact, support for exclusive breastfeeding or other appropriate feeding, and early recognition/response to illness. Whilst increasingly accepted in both high- and low-income countries, a Cochrane review (2003) did not find evidence of KMC's mortality benefit, and did not report neonatal-specific data. **OBJECTIVES:** The objectives of this study were to review the evidence, and estimate the effect of KMC on neonatal mortality due to complications of preterm

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birth. METHODS: We conducted systematic reviews. Standardized abstraction tables were used and study quality assessed by adapted GRADE methodology. Meta-analyses were undertaken. RESULTS: We identified 15 studies reporting mortality and/or morbidity outcomes including nine randomized controlled trials (RCTs) and six observational studies all from low- or middle-income settings. Except one, all were hospital-based and included only babies of birth-weight <2000 g (assumed preterm). The one community-based trial had missing birthweight data, as well as other limitations and was excluded. Neonatal-specific data were supplied by two authors. **Meta-analysis of three RCTs commencing KMC in the first week of life showed a significant reduction in neonatal mortality [relative risk (RR) 0.49, 95% confidence interval (CI) 0.29-0.82] compared with standard care.** A meta-analysis of three observational studies also suggested significant mortality benefit (RR 0.68, 95% CI 0.58-0.79). **Five RCTs suggested significant reductions in serious morbidity for babies <2000 g (RR 0.34, 95% CI 0.17-0.65).** CONCLUSION: This is the first published meta-analysis showing that KMC substantially reduces neonatal mortality amongst preterm babies (birth weight <2000 g) in hospital, and is highly effective in reducing severe morbidity, particularly from infection. However, KMC remains unavailable at-scale in most low-income countries.

Comment

This systematic review builds on 2 previous Cochrane Reviews and a third SR evaluating the impact of KMC. This is the first SR to show a benefit on mortality.

<http://www.ncbi.nlm.nih.gov/pubmed/12804436>,
<http://www.ncbi.nlm.nih.gov/pubmed/15674932>,
<http://www.ncbi.nlm.nih.gov/pubmed/15583768>

BMC Pediatr. 2010 Apr 30;10:27.

<http://www.biomedcentral.com/1471-2431/10/27>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873519/?tool=pubmed>

Brain research to ameliorate impaired neurodevelopment--home-based intervention trial (BRAIN-HIT).

Wallander JL, McClure E, Biasini F, Goudar SS, Pasha O, Chomba E, Shearer D, Wright L, Thorsten V, Chakraborty H, Dhaded SM, Mahantshetti NS, Bellad RM, Abbasi Z, Carlo W; BRAIN-HIT Investigators.

Dhaded SM, Kore P, Mahantshetti NS, Goudar SS, Pasha O, Abbasi Z, Chomba E, Biasini F, Carlo W, Chakraborty H, Derman RJ, Care C, Goldenberg RL, McClure E, Shearer D, Thorsten V, Wallander JL, Wright LL.

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Abstract

BACKGROUND: This randomized controlled trial aims to evaluate the effects of an early developmental intervention program on the development of young children in low- and low-middle-income countries who are at risk for neurodevelopmental disability because of birth asphyxia. A group of children without perinatal complications are evaluated in the same protocol to compare the effects of early developmental intervention in healthy infants in the same communities. Birth asphyxia is the leading specific cause of neonatal mortality in low- and low-middle-income countries and is also the main cause of neonatal and long-term morbidity including mental retardation, cerebral palsy, and other neurodevelopmental disorders. Mortality and morbidity from birth asphyxia disproportionately affect more infants in low- and low-middle-income countries, particularly those from the lowest socioeconomic groups. There is evidence that relatively inexpensive programs of early developmental intervention, delivered during home visit by parent trainers, are capable of improving neurodevelopment in infants following brain insult due to birth asphyxia. **METHODS/DESIGN: This trial is a block-randomized controlled trial that has enrolled 174 children with birth asphyxia and 257 without perinatal complications, comparing early developmental intervention plus health and safety counseling to the control intervention receiving health and safety counseling only, in sites in India, Pakistan, and Zambia. The interventions are delivered in home visits every two weeks by parent trainers from 2 weeks after birth until age 36 months. The primary outcome of the trial is cognitive development, and secondary outcomes include social-emotional and motor development.** Child, parent, and family characteristics and number of home visits completed are evaluated as moderating factors. **DISCUSSION:** The trial is supervised by a trial steering committee, and an independent data monitoring committee monitors the trial. Findings from this trial have the potential to inform about strategies for reducing neurodevelopmental disabilities in at-risk young children in low and middle income countries.

Neurocysticercosis

J Neurol Sci. 2010 Jan 15;288(1-2):135-41. Epub 2009 Oct 28.

Natural history of solitary cerebral cysticercosis on serial magnetic resonance imaging and the effect of albendazole therapy on its evolution.

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Abstract

AIM: To describe the evolution of imaging characteristics of solitary cerebral cysticercal lesions (SCCL) on serial MRI, and to study the effect of treatment with albendazole. **DESIGN:** Randomised controlled prospective trial. **METHODS AND MATERIAL: 123 patients with new-onset seizures and SCCL on contrast MRI were randomised to treatment with albendazole and followed with up to five serial MRIs.** **RESULTS:** 81 patients (M - 41, F - 40) with mean age of 19.6+/-11.7years and 4 or 5 serial MRI were included in the analysis. Analysis

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was performed on 356 MRI's. Scolex was seen in 61.9% of patients in postcontrast T1 sequence in the first MRI study, and there was a significant drop in visibility from the next scan onwards. Cyst contents were initially T1-hypointense and T2-hyperintense with inversion on FLAIR in 30.8% and later scans showed T2-hypointensity. Cyst wall characteristics changed significantly from initially T2-hypointensity to later hyperintense rim. Initial scan revealed perilesional oedema in 98.5%, which is resolved by the second scan. Around 17.5% showed subtle perilesional T2-hyperintensity in follow-up scans. Enhancement pattern changed significantly from ring to disc, and later to non-enhancement. Initially, 69.7% lesions were in colloid-vesicular stage. Lesions moved through subsequent stages of cyst degeneration: time needed for this process is described. **Imaging characteristics, both on the first and on subsequent scans, did not differ between albendazole and control groups.** CONCLUSIONS: Evolution of SCCL follows a predictable sequence corresponding to morphologic stages described earlier, taking over a year to complete. Contrast enhancement decreases as degeneration progresses, but some calcific lesions continue to enhance. **Albendazole therapy may hasten resolution of inflammation around the lesion but affects neither the morphology of the cysticercus nor the process of degeneration and subsequent healing.**

Nutrition, micronutrients and breast feeding

(See also Maternal health, HIV case management)

Public Health Nutr. 2010 Feb;13(2):253-60. Epub 2009 Aug 4.

Evaluation of a kindergarten-based nutrition education intervention for pre-school children in China.

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Abstract

OBJECTIVE: To evaluate the impact of nutrition education in kindergartens and to promote healthy dietary habits in children. **DESIGN:** Prospective cohort study. Four kindergartens with 1252 children were randomized to the intervention group and three with 850 children to the control group. The personal nutritional knowledge, attitudes and dietary behaviours of the parents were also investigated. **Each month, children and parents in the intervention group participated in nutrition education activities. The main outcome measures were anthropometrics and diet-related behaviours of the children and the nutritional knowledge and attitudes of the parents at baseline, 6 months (mid-term) and 1 year (post-test).** Baseline demographic and socio-economic characteristics were also collected. **SETTING:** Seven kindergartens from Hefei, the capital city of Anhui Province, eastern China. **SUBJECTS:** Two thousand one hundred and two 4- to 6-year-old pre-schoolers from seven kindergartens participated. **RESULTS:** **The prevalence of children's unhealthy diet-related behaviours decreased significantly and good lifestyle behaviours increased in the group receiving nutrition education compared with controls. Parental eating habits and attitudes to**

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planning their children's diets also changed appreciably in the intervention group compared with the control group ($P < 0.05$). However, there were no statistically significant differences in children's height, weight, height-for-age Z-score or weight-for-age Z-score between the two groups. CONCLUSIONS: Kindergarten-based nutrition education improves pre-schoolers' lifestyle behaviours and brings about beneficial changes in parents' attitudes to planning their children's diets and their own personal eating habits.

J Nutr. 2009 Sep;139(9):1738-43. Epub 2009 Jul 8.

A responsive feeding intervention increases children's self-feeding and maternal responsiveness but not weight gain.

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Abstract

Responsive complementary feeding, whereby the mother feeds her child in response to child cues and psychomotor abilities, is low in some countries and likely contributes to malnutrition. Interventions are needed to evaluate whether promoting responsive feeding would add any benefit. Using a cluster-randomized field trial, we evaluated a 6-session educational program that emphasized the practice of child self-feeding and maternal responsiveness. **A total of 108 mothers and their 8- to 20-mo-old children in 19 clusters were randomly assigned to the intervention group and 95 in 18 clusters were assigned to the informational control group.** Outcomes were assessed at pretest, postintervention, and follow-up. Research assistants, who were unaware of group assignment, observed and coded mother and child midday meal behaviors. **At follow-up, the percent of self-fed mouthfuls was 47.8 +/- 42.4 (mean +/- SD) in the responsive feeding group children compared with 32.2 +/- 41.0 in the controls ($P = 0.01$); likewise, the number of responsive verbalizations was 6.55 +/- 5.9 in the responsive feeding mothers and 4.62 +/- 4.5 in controls ($P = 0.01$). Intervention mothers recalled more messages.** Mouthfuls of food eaten by children and weight were equivalent in the 2 groups. Lack of change in foods eaten and small quantities may explain the similarly low levels of weight gain. These results provide evidence that self-feeding and maternal verbal responsiveness, two developmentally important behaviors, can be increased by targeting specific behaviors with appropriate behavior change strategies of modeling and coached practice. Weight gain may require more nutritional input, especially in areas of high food insecurity.

Micronutrients and food fortification

(see also Anaemia)

C Public Health. 2010 Mar 18;10:145.

<http://www.biomedcentral.com/1471-2458/10/145>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2847544/?tool=pubmed>

Effect on longitudinal growth and anemia of zinc or multiple micronutrients added to vitamin A: a randomized controlled trial in children aged 6-24 months.

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Abstract

BACKGROUND: The benefits of zinc or multiple micronutrient supplementations in African children are uncertain. African children may differ from other populations of children in developing countries because of differences in the prevalence of zinc deficiency, low birth weight and preterm delivery, recurrent or chronic infections such as HIV, or the quality of complementary diets and genetic polymorphisms affecting iron metabolism. **The aim of this study was to ascertain whether adding zinc or multiple micronutrients to vitamin A supplementation improves longitudinal growth or reduces prevalence of anemia in children aged 6-24 months.** **METHODS:** Randomized, controlled double-blinded trial of prophylactic micronutrient supplementation to children aged 6-24 months. Children in three cohorts - 32 HIV-infected children, 154 HIV-uninfected children born to HIV-infected mothers, and 187 uninfected children born to HIV-uninfected mothers - were separately randomly assigned to receive daily vitamin A (VA) [n = 124], vitamin A plus zinc (VAZ) [n = 123], or multiple micronutrients that included vitamin A and zinc (MM) [n = 126]. **RESULTS: Among all children there were no significant differences between intervention arms in length-for-age Z scores (LAZ) changes over 18 months. Among stunted children (LAZ below -2) [n = 62], those receiving MM had a 0.7 Z-score improvement in LAZ versus declines of 0.3 in VAZ and 0.2 in VA (P = 0.029 when comparing effects of treatment over time).** In the 154 HIV-uninfected children, MM ameliorated the effect of repeated diarrhea on growth. Among those experiencing more than six episodes, those receiving MM had no decline in LAZ compared to 0.5 and 0.6 Z-score declines in children receiving VAZ and VA respectively (P = 0.06 for treatment by time interaction). **After 12 months, there was 24% reduction in proportion of children with anemia (hemoglobin below 11 g/dL) in MM arm (P = 0.001), 11% in VAZ (P = 0.131) and 18% in VA (P = 0.019).** Although the within arm changes were significant; the between-group differences were not significant. **CONCLUSIONS: Daily multiple micronutrient supplementation combined with vitamin A was beneficial in**

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improving growth among children with stunting, compared to vitamin A alone or to vitamin A plus zinc. Effects on anemia require further study.

Int J Vitam Nutr Res. 2009 Sep;79(5-6):348-61.

Impact of a multiple-micronutrient fortified salt on the nutritional status and memory of schoolchildren.

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Abstract

OBJECTIVE: This study was conducted to test the efficacy of a multiple micronutrient-fortified cooking salt. **METHODS:** A randomized controlled trial with a pre- and post-test design was used to study children 5 to 18 years of age, with an experimental (n=213) and control group (n=189). The children were sampled from 3 residential schools and were studied for 9 months. **The experimental group received a multiple micronutrient-fortified salt containing vitamins A, B(1), B(2), B(6), B(12), as well as folic acid, niacin, iron, iodine, and zinc. The control group received iodized salt.** Biochemical measurements [hemoglobin, serum ferritin (SF), serum transferrin receptor (sTfR), C-reactive protein (CRP), alpha-1 acid glycoprotein (AGP), serum retinol, serum vitamin B(12), serum folic acid, serum zinc, and urinary iodine (UI)] were measured at baseline and post-intervention. Hemoglobin was measured in all the children three times during the study period, while the remaining biochemical measurements were performed in a subsample of children. Children between 11 and 18 years of age were given cognitive tests to assess memory and attention. **RESULTS: There was a significant improvement (p<0.05) in all the biochemical measurements and memory tests in the experimental group when compared with the control group. Post-intervention in the experimental group, the increase in hemoglobin was 0.67 g/dL (p<0.05). Iron status and body iron stores increased significantly (p<0.05) in the experimental group compared to the control group, while serum zinc increased by 50 mug/dL (p<0.05), and the prevalence of retinol deficiency decreased from 57.1 % at baseline to 16 % post-intervention (p<0.05).** **CONCLUSION:** The multiple micronutrients from the multiple micronutrient-fortified cooking salt were absorbed in the children and helped in combating micronutrient deficiencies.

Appetite. 2010 Feb;54(1):150-5. Epub 2009 Oct 6.

Improved appetite after multi-micronutrient supplementation for six months in HIV-infected South African children.

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Abstract

The aim of the study was to assess the effect of multi-micronutrient supplementation on the appetite of HIV-infected children. HIV-infected children (6-24 months) who had previously been hospitalized were enrolled into a double-blind randomized trial, and given daily multi-micronutrient supplements or placebos for six months. Appetite tests were performed at enrollment and after three and six months. Appetite was measured as ad libitum intake of a commercial cereal test food served after an overnight fast according to standardized procedures. Body weights and total amount of test food eaten were measured. In total, 99 children completed the study (50 on supplements and 49 on placebos). Amounts eaten per kilogram body weight in the supplement group at enrollment and after six months were 36.7 \pm 17.7 g/kg (mean \pm SD) and 41.3 \pm 15.0 g/kg respectively, while the amounts in the placebo group were 47.1 \pm 14.9 g/kg and 45.7 \pm 13.1 g/kg respectively. The change in amount eaten per kilogram body weight over six months was significantly higher in the supplement group (4.7 \pm 14.7 g/kg) than in the placebo group (-1.4 \pm 15.1 g/kg). **Multi-micronutrient supplementation for six months seems to significantly improve the appetite of HIV-infected children.**

Breastfeeding and Complimentary feeding

Am J Clin Nutr. 2009 Oct;90(4):1070-4. Epub 2009 Aug 26.

Health and development outcomes in 6.5-y-old children breastfed exclusively for 3 or 6 mo.

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Abstract

BACKGROUND: Despite the current World Health Organization recommendation that infants be exclusively breastfed for 6 mo, this practice remains unusual in both developed and developing countries. **OBJECTIVE:** The objective was to compare health and development outcomes at age 6.5 y in children who were exclusively breastfed for 3 mo (EBF3) or for 6 mo (EBF6); in the EBF3 group, the children continued partial breastfeeding for > or =6 mo. **DESIGN:** This was a prospective cohort study nested within a large, cluster-randomized trial of a breastfeeding promotion intervention in the Republic of Belarus. Outcomes compared at 6.5 y included anthropometric measurements, systolic and diastolic blood pressure, intelligence quotient, teachers' ratings of academic performance, parent- and teacher-rated behavior, atopic symptoms, allergen skin-prick tests, and dental caries. All statistical analyses were adjusted for cluster- and individual-level covariates and for clustering of outcomes within the clinics at which the children were examined. **RESULTS:** The 2427 EBF3 and 524 EBF6 children who were followed up represented 84.7% and 89.4%, respectively, of those followed for the first year of life. **The only significant differences observed between the 2 groups were in mean body mass index, triceps skinfold thickness, and hip circumference, all of which were higher in the EBF6 group.** **CONCLUSIONS:** We observed no demonstrable beneficial or adverse long-term effects on child health of exclusive breastfeeding for 6 mo. Higher

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adiposity measures in the EBF6 group probably reflect reverse causality rather than a causal effect of prolonged exclusive breastfeeding. Established benefits appear to be limited to the period of exclusive breastfeeding.

Comment

This was not an RCT of breastfeeding duration, but a nested cohort study within an RCT of the Baby Friendly Hospital Initiative. The hospitals were randomised to a breastfeeding promotion intervention modeled on the WHO/UNICEF Baby-Friendly Hospital Initiative (experimental group) or to continue the maternity hospital and polyclinic practices. Therefore the breastfeeding duration was based on the mother's choice after exposure to the different hospital practice, and the outcomes may be affected by confounding.

Public Health Nutr. 2010 Apr;13(4):556-65. Epub 2009 Aug 26.

Effectiveness of an educational intervention on complementary feeding practices and growth in rural China: a cluster randomised controlled trial.

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Abstract

OBJECTIVE: Inappropriate complementary feeding is one of the major causes of malnutrition in young children in developing countries. We developed an educational intervention, delivered by local health-care providers, aimed at improving complementary feeding practices and child nutrition. **DESIGN:** Eight townships in Laishui, a rural area in China, were randomly assigned to the educational intervention or control group. A total of 599 healthy infants were enrolled at age 2-4 months and followed up until 1 year of age. **In the intervention group, educational messages and enhanced home-prepared recipes were disseminated to caregivers through group trainings and home visits.** Questionnaire surveys and anthropometric measurements were taken at baseline and ages 6, 9 and 12 months. Analysis was by intention to treat.

RESULTS: It was found that food diversity, meal frequency and hygiene practices were improved in the intervention group. Infants in the intervention group gained 0.22 kg more weight (95 % CI 0.003, 0.45 kg, P = 0.047) and gained 0.66 cm more length (95 % CI 0.03, 1.29 cm, P = 0.04) than did controls over the study period. **CONCLUSIONS:** Findings from the study suggest that an educational intervention delivered through local health-care providers can lead to substantial behavioural changes of caregivers and improve infant growth.

Breastfeed Rev. 2009 Nov;17(3):5-10.

When and why Filipino mothers of term low birth weight infants interrupted breastfeeding exclusively.

Agrasada GV, Kylberg E.

Randomised trials in child health in developing countries 2009-10

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Abstract

This paper makes use of data collected in a randomised controlled trial that was designed to test the efficacy of postpartum breastfeeding counselling to increase exclusive breastfeeding among term low birth weight infants in Manila during the first six months. **Mothers were randomised to a control group or one of two home visit interventions: by trained breastfeeding counsellors or child care counsellors without breastfeeding support training. Sixty mothers received peer breastfeeding counselling while a further 119 mothers did not. The median duration of exclusive breastfeeding among mothers who received counselling was five weeks versus two weeks among those who received no counselling (p<0.001).** Exclusive breastfeeding was interrupted to offer infants water, traditional herbal extracts or artificial baby milk. Mothers who interrupted exclusive breastfeeding claimed they had insufficient milk or that their infants had slow weight gain. Early and sustained breastfeeding support will enable mothers to exclusively breastfeed low birth weight infants for the first six months.

Prev Med. 2009 Dec;49(6):529-34. Epub 2009 Oct 19.

Using the theory of planned behavior to examine effectiveness of an educational intervention on infant feeding in China.

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Abstract

OBJECTIVE: To determine the effectiveness of an educational intervention on infant feeding behaviors and mothers' psychosocial mediating variables based on the Theory of Planned Behavior (TPB), and to assess the predictive effect of mediating variables on mothers' intention and feeding practices. **METHODS:** We did a **cluster-randomized trial in 8 paired townships of Laishui County, China during 2006-2007. 599 mothers with infants aged 2-4-mo were enrolled at the baseline survey, of whom 485 were followed up after 11-mo intervention.** **RESULTS:** The intervention group had significantly higher scores than controls in knowledge, attitudes, self-efficacy, intention, norm beliefs, as well as feeding behaviors (Hotellings T-square=143.96, P<0.01). Mothers' intention towards recommended feeding behaviors was positively associated with mothers' attitudes, subjective norms and self-efficacy at baseline, and was associated with their attitudes, self-efficacy, and knowledge at post-intervention evaluation. Intervention, mothers' knowledge, intention and subjective norm of villagers were independent predictors of their feeding behaviors after intervention. **CONCLUSIONS:** Findings from this study suggested that TPB is an appropriate theory for explaining the effect of psychosocial factors such as knowledge, attitudes, self-efficacy, subjective norms, and intentions on infant feeding behaviors, and a useful guideline to design the targets and key approaches for infant feeding interventions.

Oncology

J Clin Oncol. 2010 Apr 10;28(11):1911-8. Epub 2010 Mar 8.

Benefits of the intermittent use of 6-mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in children: randomized trial from the Brazilian Childhood Cooperative Group-protocol ALL-99.

Brandalise SR, Pinheiro VR, Aguiar SS, Matsuda EI, Otubo R, Yunes JA, Pereira WV, Carvalho EG, Cristofani LM, Souza MS, Lee ML, Dobbin JA, Pombo-de-Oliveira MS, Lopes LF, Melnikoff KN, Brunetto AL, Tone LG, Scrideli CA, Morais VL, Viana MB.

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Abstract

PURPOSE To describe event-free survival (EFS) and toxicities in children with low-risk acute lymphoblastic leukemia (ALL) assigned to receive either continuous 6-mercaptopurine (6-MP) and weekly methotrexate (MTX) or intermittent 6-MP with intermediate-dose MTX, as maintenance treatment. **PATIENTS AND METHODS** Between October 1, 2000, and December 31, 2007, 635 patients with low-risk ALL were enrolled onto Brazilian Childhood Cooperative Group for ALL Treatment (GBTLI) ALL-99 protocol. **Eligible children (n = 544) were randomly allocated to receive either continuous 6-MP/MTX (group 1, n = 272) or intermittent 6-MP (100 mg/m²/d for 10 days, with 11 days resting) and MTX (200 mg/m²) every 3 weeks; group 2, n = 272).** **RESULTS** The 5-year overall survival (OS) and EFS were 92.5% +/- 1.5% SE and 83.6% +/- 2.1% SE, respectively. According to maintenance regimen, the OS was 91.4% +/- 2.2% SE (group 1) and 93.6% +/- 2.1% SE (group 2; P = .28) and EFS 80.9% +/- 3.2% SE (group 1) and 86.5% +/- 2.8% SE (group 2; P = .089). Remarkably, the intermittent regimen led to significantly higher EFS among boys (85.7% v 74.9% SE; P = .027), while no difference was seen for girls (87.0% v 88.8% SE; P = .78). Toxic episodes were recorded in 226 and 237 children, respectively. Grade 3 to 4 toxic events for groups 1 and 2 were, respectively, 273 and 166 for hepatic dysfunction (P = .002), and 772 and 636 for hematologic episodes (P = .005). Deaths on maintenance were: seven (group 1) and one (group 2). **CONCLUSION** The intermittent use of 6-MP and MTX in maintenance is a less toxic regimen, with a trend toward better long-term EFS. Boys treated with the intermittent schedule had significantly better EFS.

J Pediatr Hematol Oncol. 2009 Sep;31(9):635-41.

Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia.

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Randomised trials in child health in developing countries 2009-10

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Abstract

BACKGROUND: Outpatient oral therapy is infrequently used in pediatric low-risk febrile neutropenia (LRFN) as there is insufficient data regarding its equivalence as compared with parenteral therapy. **METHODS:** This is a single institutional, randomized control trial in pediatric LRFN aged 2 to 15 years, in which **123 episodes in 88 patients were randomized to outpatient oral ofloxacin 7.5 mg/kg 12 hourly and amoxicillin-clavulanate 12.5 mg/kg 8 hourly or outpatient intravenous (IV) ceftriaxone 75 mg/kg and amikacin 15 mg/kg once daily after blood cultures.** **RESULTS:** Out of 119 evaluable episodes, one-third were leukemia patients in maintenance and rest were solid tumors. **Success was achieved in 55/61 (90.16%) and 54/58 (93.1%) in oral and IV arms, respectively, (P=0.56).** There were 3 hospitalizations but no mortality. Median days to resolution of fever, absolute neutrophil count >500/mm³ and antibiotic use were 3, 5, and 6 days in both arms. There were 5 blood culture isolates (3 gram-positive and 2 gram-negative bacteria). Failure of outpatient therapy was associated with perianal infections, bacteremia, febrile neutropenia onset before day 9 of chemotherapy in solid tumors and Vincristine, actinomycin-D, and cyclophosphamide chemotherapy for rhabdomyosarcoma. **All gram-positive isolates were successes, whereas both gram-negative isolates were failures.** Diarrhea in IV arm and Vincristine, actinomycin-D, and cyclophosphamide chemotherapy in the oral arm predicted failure in subgroup analysis. **CONCLUSIONS:** Outpatient therapy is efficacious and safe in pediatric LRFN. There was no difference in outcome in oral versus IV outpatient therapy. Amoxicillin-clavulanate and ofloxacin may be the oral regimen of choice.

Ophthalmology

*** JAMA. 2009 Sep 2;302(9):962-8.

<http://jama.ama-assn.org/cgi/content/full/302/9/962>

Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: a randomized trial.

Porco TC, Gebre T, Ayele B, House J, Keenan J, Zhou Z, Hong KC, Stoller N, Ray KJ, Emerson P, Gaynor BD, Lietman TM.

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Abstract

CONTEXT: Mass oral azithromycin distribution to affected communities is a cornerstone of the World Health Organization's trachoma elimination program. Antibiotics are provided to target the ocular strains of chlamydia that cause trachoma, but may also be efficacious against respiratory disease, diarrhea, and malaria--frequent causes of childhood mortality in trachoma-

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endemic areas. **OBJECTIVE: To compare mortality rates of participants aged 1 to 9 years in treated communities with those in untreated communities.** **DESIGN, SETTING, AND PARTICIPANTS:** We conducted a cluster-randomized clinical trial of mass azithromycin administration for trachoma control. Forty-eight communities (known as subkebeles) were randomized into 1 of 3 treatment schedules (annual treatment of all residents [15,902 participants], biannual treatment of all residents [17,288 participants], or quarterly treatment of children only [14,716 participants]) or into 1 group for which treatment was delayed by 1 year (control, 18,498 participants). Twelve subkebeles were randomized to each of the 4 schedules with all children in each of the 3 communities being eligible for treatment. The trial was conducted in a field setting in rural Ethiopia, May 2006 to May 2007. **INTERVENTIONS:** A single dose of oral azithromycin (adults, 1 g; children, 20 mg/kg) was administered for treatment of ocular Chlamydia trachomatis infection. Antibiotic coverage levels for children aged 1 to 9 years exceeded 80% at all visits. **MAIN OUTCOME MEASURE:** The main outcome measure was the community-specific mortality risk for children aged 1 to 9 years over the course of 1 year. Mortality was measured by enumerative census at baseline and again after 1 year. Comparison of the risk of mortality was a prespecified outcome for the clinical trial. **RESULTS: The odds ratio for childhood mortality in the intervention communities was 0.51 (95% confidence interval, 0.29-0.90; P = .02; clustered logistic regression) compared with the control group. In the treated communities, the estimated overall mortality rate during this period for children aged 1 to 9 years in the untreated group was 8.3 per 1000 person-years (95% confidence interval, 5.3-13.1), while among the treated communities, the estimated overall mortality rate was 4.1 per 1000 person-years (95% confidence interval, 3.0-5.7) for children aged 1 to 9 years.** **CONCLUSION:** In a trachoma-endemic area, mass distribution of oral azithromycin was associated with reduced mortality in children.

Comment

This is a very important trial, although unblinded this is evidence that the mass administration of a single dose of an antibiotic can reduce child mortality. This study only gave azithromycin to children 1-9 years of age. In support of a true effect of the intervention, there was no significant mortality difference among untreated infants in the treatment and control groups, suggesting that the observed differences in the 1- to 9-year olds were unlikely to have resulted from chance variation or confounding.

In some countries the effect of mass administration of one dose of azithromycin might be justified because of trachoma. In other countries it might be justified because of the high prevalence of infected scabies, and this might prevent deaths from other common causes as was found in this large study. Many countries carry out supplemental immunization activities (SIA) that deliver measles vaccine, oral polio vaccine, vitamin A and albendazole. Adding a single dose of azithromycin might provide some protection for poor children in remote areas who would otherwise never get to see a health worker.

Ophthalmology. 2009 Nov;116(11):2047-50. Epub 2009 Sep 10.

Complete local elimination of infectious trachoma from severely affected communities after six biannual mass azithromycin distributions.

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Abstract

OBJECTIVE: To determine whether infectious trachoma can be completely eliminated from severely affected villages. **DESIGN:** Cross-sectional survey of 2 villages previously enrolled and monitored over 42 months as part of a larger, group-randomized clinical trial. **PARTICIPANTS:** A total of 758 individuals residing in 2 villages with high baseline trachoma prevalence, of a total population of 768 (98.7%). **METHODS:** **All members of the 2 villages were offered 6 biannual mass treatments with oral azithromycin.** At 42 months, each current village member was examined. The right upper tarsal conjunctiva was everted and swabbed. Samples were processed for evidence of *Chlamydia trachomatis* RNA. **MAIN OUTCOME MEASURES:** Clinical activity by World Health Organization simplified grading scale for trachoma and laboratory evidence of chlamydial RNA. **RESULTS:** Average antibiotic coverage over the study period was 90% and 94% in the 2 villages. **Clinical trachoma activity in children aged 1 to 5 years decreased from 78% and 83% in the 2 villages before treatment to 17% and 24% at 42 months.** Polymerase chain reaction (PCR) evidence of infection in the same age group decreased from 48% to 0% in both villages at 42 months. **When all age groups were examined, there were zero cases with evidence of chlamydial RNA among 758 total villagers tested.** **CONCLUSIONS:** **Biannual mass distribution of azithromycin can locally eliminate ocular chlamydial infection from severely affected communities.**

Trop Med Int Health. 2010 Jan;15(1):98-104.

How much is not enough? A community randomized trial of a Water and Health Education programme for Trachoma and Ocular *C. trachomatis* infection in Niger.

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Abstract

SUMMARY OBJECTIVE: To determine the impact after 2 years of a water and health education (W/HE) programme on ocular *Chlamydia trachomatis* infection and trachoma. **METHODS:** We randomized 12 trachoma-endemic communities in Maradi, Niger 1:1 to W/HE intervention and control arms and collected data on 10 of the 12 villages. In the intervention villages, at least one clean water well was constructed, and a 3 month, modest health education programme was provided immediately prior to the 2 year survey. We censused all households, and 557 children ages 1-5 years were randomly selected as sentinel children and examined at baseline and at one and 2 years from baseline. Trachoma was clinically assessed and a swab taken and analyzed for *C. trachomatis*. Tetracycline eye ointment was provided to all children in either arm during the surveys who had signs of trachoma. **RESULTS:** Infection with *C. trachomatis* declined slightly, and not significantly, in the children in the control villages over

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the 2 years, from 15% to 11%. The decline in infection was more pronounced, and significant, in the children in the intervention villages, from 26% to 15%. However, the change in infection rates in the intervention villages was not significantly different from the change in infection rates in the control villages ($P = 0.39$, and 0.11 for change from baseline to 1 year and 2 year, respectively). There was also no difference in the change in overall trachoma rates between the two arms. **CONCLUSION: These data suggest that the provision of water plus a modest health education programme did not result in a significant difference in trachoma or ocular *C. trachomatis* infection in endemic communities in Niger.** A more substantial health education intervention is likely necessary to produce change.

Am J Trop Med Hyg. 2010 Mar;82(3):482-7.

Clinical activity and polymerase chain reaction evidence of chlamydial infection after repeated mass antibiotic treatments for trachoma.

Keenan JD, Lakew T, Alemayehu W, Melese M, Porco TC, Yi E, House JI, Zhou Z, Ray KJ, Acharya NR, Whitcher JP, Gaynor BD, Lietman TM.

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Abstract

It is unclear how the prevalence of clinically active trachoma correlates with the prevalence of ocular chlamydial infection at the community level. In 24 villages from a cluster-randomized clinical trial of mass azithromycin distributions in Ethiopia, the correlation between the prevalence of clinical activity (on examination) and chlamydial infection (by polymerase chain reaction) was moderately strong before mass antibiotic treatments (Pearson's correlation coefficient $r = 0.75$, 95% confidence interval [CI] = 0.52-0.87), but decreased at each time point during four biannual treatments (at 24 months, $r = 0.15$, 95% CI = -0.14-0.41). One year after the final treatment, the correlation coefficient had increased, but not to the pre-treatment level ($r = 0.55$, 95% CI = 0.30-0.73). In a region with hyperendemic trachoma, conjunctival examination was a useful indicator of the prevalence of chlamydial infection before treatments, less useful during mass treatments, but regained utility by one year after treatments had stopped.

Ophthalmology. 2009 Oct;116(10):1839-45. Epub 2009 Jul 9.

A randomized, clinical trial evaluating ready-made and custom spectacles delivered via a school-based screening program in China.

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Abstract

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PURPOSE: We sought to evaluate visual performance and satisfaction with ready-made spectacles (RMS) in Chinese school-aged children with uncorrected refractive error. **DESIGN:** Randomized, double-blind, clinical trial. **PARTICIPANTS:** Junior high school students from urban Guangzhou, China, aged approximately 12 to 15 years with ≥ 1 diopter (D) of uncorrected spherical equivalent (SE) refractive error. Students were excluded with ≥ 2.00 D astigmatism, ≥ 2 D myopic anisometropia, and ≥ 1 D hyperopic anisometropia and ocular disease affecting vision. **METHODS:** Refractive error was determined by cycloplegic subjective refraction. Students were randomly assigned to receive RMS or custom spectacles (CS) and assessed after 1 month of use. We required 175 students to complete in each arm to be able to measure a 15% difference in compliance. **MAIN OUTCOME MEASURES:** Compliance with spectacles lens wear, patterns of use, vision, symptoms, and perceived value. **RESULTS:** Screening identified 965 of 4607 (20.9%) students with reduced distance vision; 212 of the 965 (22.0%) refused evaluation and 187 of the 965 (20.8%) had < 1 D of SE refractive error. Sixty-one (6.3%) were referred for further evaluation and the remaining 495 (51.3%) participated. Social, demographic, and ocular parameters were similar in the 2 groups. Average SE refractive error was -2.57 ± 1.31 (mean value \pm standard deviation [SD]). Spectacle vision (Snellen acuity, mean \pm SD) was worse with RMS in the eye with lower SE (20/25(-0.5) \pm 0.9 lines vs 20/25(+1) \pm 0.7 lines; $P = 0.004$) and higher SE (20/25(-2) \pm 1.2 lines vs 20/25(+1) \pm 0.8; $P < 0.001$). There were no differences ($P > 0.05$) in the rate of use (94.3% vs 92.2%), wearing to the 1-month visit (46.9% vs 51.5%), planned use (93.3% vs 93.7%), value (89.5% vs 91.7% "moderate or high value or most valued possession"), or symptoms (blur, 21.1% vs 19.4% [$P = 0.8$] and other symptoms [$P > 0.2$]). **CONCLUSIONS:** Although visual acuity was better with CS, no difference was found in acceptability in this population of students with predominantly simple myopic refractive error. This study supports the use of RMS in a school-based refractive services program, saving costs and improving the logistics of service delivery.

Orbit. 2010 Feb;29(1):29-34.

Levator plication versus resection in congenital ptosis - a prospective comparative study.

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Abstract

PURPOSE: To compare levator plication with resection in congenital ptosis. **METHODS:** Prospective comparative randomized trial involving 20 eyes of 20 patients with age > 4 yrs, simple mild-to-moderate congenital ptosis with good-to-fair amount of levator action were included. Patients were randomized to either levator resection or plication. Outcome was compared in terms of eyelid height and course of postoperative events. Data was compared using the paired and unpaired t-test. **RESULTS:** The mean M.R.D. 1 at the end of 3 months in Group A was 2.8 ± 1.23 mm and in Group B was 1.12 ± 0.83 mm (p value = 0.001). Plication did not improve levator action much. Resection lead to more alterations in Bell's, lid lag, lagophthalmos and persisting edema (3 cases). **CONCLUSION:** In 70% cases of congenital ptosis, good cosmetic outcome can be achieved with levator resection. With levator plication

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there are greater chances of drooping from fourth week onwards. The technique of plication, though simpler in approach failed to correct dystrophic muscle in congenital ptosis.

Br J Anaesth. 2009 Nov;103(5):739-43. Epub 2009 Aug 25.

Comparison of sub-Tenon's block with i.v. fentanyl for paediatric vitreoretinal surgery.

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Abstract

BACKGROUND: Vitreoretinal (VR) surgery is associated with moderate to severe pain and significant postoperative nausea and vomiting (PONV). The study aimed to assess the effectiveness of sub-Tenon's block for providing perioperative analgesia in children undergoing VR surgery. **METHODS:** In a randomized, observer-blinded trial, after obtaining institutional ethical committee approval and parental consent, 200 ASA grade I-II children aged 5-16 yr were allocated to receive either a sub-Tenon's block (Group SB) or 2 microg kg(-1) i.v. fentanyl (Group F) after induction of anaesthesia and topical anaesthesia of the conjunctiva with proparacaine 0.5% drops. Patients in Group F received fentanyl 0.5 microg kg(-1) and those in Group SB were given a corresponding volume of normal saline i.v. every hour from preloaded syringes. Increases in heart rate or mean arterial pressure by more than 20% of baseline were treated with additional 0.5 microg kg(-1) i.v. fentanyl boluses in both groups. The incidence of oculocardiac reflex (OCR), need for additional analgesics, postoperative pain, and PONV were recorded for the first 24 h after surgery. **RESULTS:** More patients in Group F (47.96%) had moderate to severe pain in the first 24 h when compared with Group SB (31.36%) (P=0.023). The need for postoperative ibuprofen was higher in Group F (66.3%) compared with Group SB (47.95%) (P=0.012). The incidence of OCR was significantly higher in Group F (31.6%) compared with Group SB (5.1%) (P<0.001). The incidence of PONV was similar in both groups. **CONCLUSIONS:** Sub-Tenon's block provides more effective analgesia than i.v. fentanyl for paediatric VR surgery.

Oral health / dentistry

Int J Paediatr Dent. 2009 Nov;19(6):423-30. Epub 2009 Sep 1.

Influence of the cavity-size on the survival rate of proximal ART restorations in primary molars.

Kemoli AM, van Amerongen WE.

Randomised trials in child health in developing countries 2009-10

Department of Paediatric Dentistry/Orthodontics University of Nairobi, Kenya.

Abstract

Aim: To evaluate the influence of the size of proximal cavities on the survival rate of the atraumatic restorative treatment (ART) restorations. **DESIGN:** A total of 804 children, aged 6-8 years, from a low socio-economic community, with an ART restorable proximal carious lesion in their primary molars, participated. Over a 3-week period, three 'experienced' and four 'inexperienced' operators randomly paired with four 'experienced' and four 'inexperienced' assistants, made the restorations at site using hand instruments. They randomly used Fuji IX, Ketac Molar Easymix and Ketac Molar Aplicap glass ionomer cements to restore the cavities, under randomly selected rubber dam and cotton roll isolation methods. The fillings were independently evaluated by nine trained and calibrated evaluators. **RESULTS:** After 1 year, the survival rate of the fillings evaluated in the study was 44.8%. Irrespective of the other factors involved, restorations with the highest survival rate were of size between 2 and 3 mm (mesio-distal, bucco-lingual, and depth) or volumes 10.0-19.9 mm³ (Chi-square, $P = 0.002$, KM mean survival of 345 days). **CONCLUSIONS:** While the survival rates for class II ART restorations were still low, the choice of medium-sized proximal cavities gave better survival rates for this technique.

J Contemp Dent Pract. 2009 Jul 1;10(4):26-34.

Clinical evaluation of polyamide polymer burs for selective carious dentin removal.

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Abstract

AIM: The aim of this study was to evaluate the carious dentin removal efficacy of new rotary polyamide burs capable of selectively removing infected dentin without removing sound dentin. **METHODS AND MATERIALS:** This study included 40 subjects with bilateral occlusal carious lesions on mandibular first permanent molars. The lesions were randomly assigned to receive one restoration after carious dentin removal with a polymer bur and the second after removal of carious dentin with a carbon steel round bur. Both procedures were completed by a single operator in one appointment. The efficacy of caries removal, time taken for caries removal, and patients' perception of the treatment were evaluated. The restorations were evaluated immediately and after six months using intraoral periapical radiographs (IOPA). **RESULTS:** The results revealed statistically significant differences between the polymer burs and carbon steel burs with respect to caries removal efficacy ($p < 0.001$) and the time taken for caries removal ($p < 0.001$). No statistically significant results were obtained regarding patients' perception of the treatment and longevity of the restorations. **CONCLUSION:** Carbon steel round burs remove caries lesions more efficiently than polymer burs but they tend to contribute to the over-preparation of the cavity. Polyamide burs were found to be self-limiting and lose their cutting efficiency on reaching affected dentin and do not cut sound dentin. The time required for caries removal using the polymer bur was significantly longer than when using a carbon steel round bur. **CLINICAL SIGNIFICANCE:** One of the goals of conservative dentistry is to develop a method for removing caries-infected dentin while preserving caries-unaffected

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dentin. The use of polymer burs appears to offer a straightforward and efficient means for achieving this goal and conserving healthy tooth structure.

Caries Res. 2009;43(6):430-5. Epub 2009 Oct 28.

Study of the efficacy of toothpaste containing casein phosphopeptide in the prevention of dental caries: a randomized controlled trial in 12- to 15-year-old high caries risk children in Bangalore, India.

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Abstract

Casein phosphopeptide (CPP) has the potential to be added to mouth rinses, gels, toothpastes, chewing gums and confectioneries. Until now CPP has been studied in vitro, in situ and in animals, but clinical trials are lacking. This study was conducted to evaluate the efficacy of CPP-containing toothpaste in preventing dental caries in schoolchildren. The study was conducted among 150 schoolchildren randomly divided into three groups, each using one of three types of toothpastes: (a) containing 2% w/w CPP; (b) containing 1,190 mg/kg fluoride as 0.76% sodium monofluorophosphate (SMFP); (c) placebo toothpaste without CPP or fluoride. Students brushed with the given toothpastes for 24 months. Oral hygiene and caries experience were assessed at baseline, 12 and 24 months. The increments in caries lesions were calculated and analyzed to assess the caries-preventive effect. A significant reduction in caries increment was observed among students using CPP toothpaste or SMFP toothpaste, compared with the group using the placebo toothpaste. The reduction in caries increment was not significantly different between the CPP and SMFP groups. Oral Hygiene Index score increased from the 12-month to the 24-month examination. It is concluded that CPP can be effectively incorporated into calcium carbonate-based toothpaste and that toothpaste containing CPP is effective in preventing caries. Toothpaste containing 2% CPP seemed to have an efficacy similar to paste containing 1,190 mg/kg SMFP in the prevention of caries. Copyright 2009 S. Karger AG, Basel.

Pain management

(See also anaesthesia and intensive care)

J Clin Nurs. 2009 Aug;18(15):2180-6.

<http://www3.interscience.wiley.com/journal/122498561/abstract?CRETRY=1&SRETRY=0>

Turkish children loved distraction: using kaleidoscope to reduce perceived pain during venipuncture.

Tüfekci FG, Celebioğlu A, Küçükoğlu S.

Randomised trials in child health in developing countries 2009-10

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Abstract

AIM: To assess the effect of distraction (looking through kaleidoscopes) to reduce perceived pain, during venipuncture in healthy school-age children. **BACKGROUND:** Distraction has been noted to be an effective method to help children cope with painful procedures. In the studies carried out, although it was found out that distraction made with different distracters reduced the pain of venipuncture, there is only one study confirming analgesic effect of distracters. **DESIGN:** The study was carried out as an intervention-control group design. **METHOD:** Children (n = 206), in whom venipuncture was applied in a laboratory for examination between the dates January-September 2006, were included in the study. The data were obtained by a form determining introductory features of the children and Wong-Baker FACES Pain Rating Scale and Visual Analogue Scale evaluating the pain. Descriptive statistics was used in the assessment of the data and t-test was used in comparisons of dependent-independent groups. **RESULTS: Pain levels of the children according to both scales in intervention group were lower than those of control group. But, it was detected that the distinction between score averages of intervention and control group of Wong-Baker FACES Pain Rating Scale, not Visual Analogue Scale, was statistically significant (p < 0.001).** **CONCLUSION:** It was detected that the distraction made with kaleidoscope effectively reduced the pain related to venipuncture in healthy school children and that some features of the children influenced the perception of pain. **RELEVANCE TO CLINICAL PRACTICE:** Distraction with kaleidoscope is a method, which the nurse will be able to use for venipuncture to obtain optimal pain control. In addition, it is important for a nurse to know some features about the children for a pain free and positive experience.

Respiratory disease: chronic

J Cyst Fibros. 2010 Jan;9(1):17-23. Epub 2009 Oct 8.

Long-term daily high and low doses of azithromycin in children with cystic fibrosis: a randomized controlled trial.

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Abstract

BACKGROUND: Long-term administration of azithromycin (AZM) in children with cystic fibrosis (CF) has improved outcomes. However, the doses and schedule of administration are not very well studied in children with CF. **METHODS:** A randomized controlled trial was conducted to compare the effect of two doses of azithromycin (5mg/kg/day and 15mg/kg/day) on FEV(1) and pulmonary exacerbations in children with cystic fibrosis. **Enrolled children were randomly allocated to receive daily azithromycin (5mg/kg/day or 15mg/kg/day) for 6months.** Clinical assessment and FEV(1) measurement were performed monthly. **RESULTS:** 56 children (28 in high dose group and 28 in low dose group) were enrolled. 47 (24 and 23

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children in low and high dose groups) completed 12 months of follow up. There was no difference in clinical scores, FEV(1), pulmonary exacerbation rates between two groups at baseline, 6 months and at 12 months. Per protocol analysis revealed that pulmonary exacerbation increased after discontinuing AZM and there was significantly more increase after 12 months of enrolment in children getting high dose azithromycin. There was no improvement in FEV(1) in either group at the end of treatment period. Children tolerated daily low as well as high dose AZM well for 6 months. There was no significant side effect of azithromycin. **CONCLUSION:** In this randomized controlled trial, we did not find differences in the effect of 2 doses (5mg/kg/day or 15mg/kg/day) of AZM on change in percentage predicted FEV(1), clinical scores, Pseudomonas colonization rates, pulmonary exacerbations and need for antibiotics. There was increase in exacerbations after stopping azithromycin in both the groups. Our results also suggest that the decrease in the incidence of LRTI persists only till 6 months after discontinuing azithromycin.

Comment

Although cystic fibrosis is rare in developing countries, the above applies to bronchiectasis (Davies Thorax 2004;59:540-541). Macrolide antibiotics exhibit immunomodulating properties. Long term, low dose erythromycin has been shown to be effective in controlling chronic suppurative airways disease

School health

(See also Nutrition, Ophthalmology)

Community Dent Oral Epidemiol. 2009 Dec;37(6):518-26. Epub 2009 Aug 20.

School-based intervention to promote preadolescents' gingival health: a community trial.

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Abstract

OBJECTIVES: Evaluation of the effectiveness of a school-based oral health promotion intervention on preadolescents' gingival health. **METHODS:** A community trial designed for a 3-month intervention study in a representative sample of 9-year-olds (n = 457) in 16 schools in Tehran, Iran. The schools were randomly assigned to three intervention groups and one control group, each group comprising two boys' and two girls' schools. **The first group of children (n = 115) received intervention via class work, solving a set of puzzles containing oral health messages, under supervision of their health counsellor. The second group (n = 114), intervention via parents, included an oral health education leaflet and a brushing diary for**

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supervising the child's tooth-brushing; the third group (n = 111) received a combination of both these interventions. The control group (n = 117) had no intervention. Effects of the intervention were assessed as changes in dental plaque and gingival bleeding. Improvements in gingival health were recorded when half of the index teeth with plaque at baseline became clean (acceptable oral hygiene) or when all index teeth with bleeding at baseline became healthy (healthy gingiva). Statistical analysis included chi square, anova, t-test, Number Needed to Treat (NNT) and generalized estimating equations (GEE). **RESULTS: At baseline, none of the children were free of plaque and all except for three boys had bleeding. After the trial, acceptable oral hygiene was more frequent in the parental-aid (P < 0.001) and the combined groups (P < 0.05), and healthy gingiva in both groups (P < 0.001) in comparison with the control group.** Outcomes in the class-work group did not differ from those in the control group. The GEE models confirmed a strong intervention effect on healthy gingiva in both groups where parents were involved: parental-aid group (OR = 7.7, 95% CI: 2.2-27.7) and combined group (OR = 6.6, 95% CI: 2.0-22.1). In all intervention groups more girls than boys achieved healthy gingiva (OR = 2.5-2.6). Parents' education showed no impact on the outcome. **CONCLUSIONS: When a school-based oral health intervention involves parents it may result in a significant improvement in the gingival health of preadolescents with poor gingival health at baseline.**

Community Dent Oral Epidemiol. 2009 Oct;37(5):391-8. Epub 2009 Jul 14.

<http://www3.interscience.wiley.com/journal/122512222/abstract>

Assessing the effectiveness of a school-based oral health promotion programme in Yichang City, China.

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Department of Preventive Dentistry, School of Stomatology, Wuhan University, Wuhan City, China.

Abstract

OBJECTIVES: To assess the outcome of oral health promotion in schoolchildren over a 3-year period in Yichang City, Hubei, China. **METHODS:** In a cluster randomized controlled trial, the concept of the World Health Organization Health Promoting Schools Project was applied to primary schoolchildren. Seven intervention schools and eight control schools were randomly selected from one district by stratified cluster sampling. The study was conducted as a 3-year follow-up study. After 3 years, 661 children remained in the intervention group and 697 children in the control group. Data on dental caries, plaque accumulation, and sulcus bleeding were collected by clinical examination, while behavioural data were gathered by self-administered questionnaires. **RESULTS: The 3-year net mean DMFS increment score was 0.22 in the intervention schools and 0.35 in the control schools (P < 0.013).** A statistically significant difference in mean plaque (P < 0.013) and sulcus bleeding (P < 0.005) increment scores after 3 years was found between the two groups. Statistically significant higher scores were observed in restorations received and sealants placed, and a lower score in untreated dental caries, in children from the intervention group than the control group after 3 years (P < 0.01). In addition, more children in the intervention schools adopted regular oral health behavioural practices such

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as brushing their teeth at least twice a day, visiting the dentist within the past calendar year, and using fluoride toothpaste. CONCLUSION: The study suggests that the school-based oral health promotion was an effective way to reduce new caries incidence, improve oral hygiene and establish positive oral health behavioural practices in the targeted schoolchildren.

Skin disease

Bull World Health Organ. 2009 Jun;87(6):424-30.

http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0042-96862009000600010&lng=en&nrm=iso&tlng=en

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2686207/?tool=pubmed>

Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial.

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Abstract

OBJECTIVE: To compare the effectiveness of oral ivermectin (IV) and two different modalities of topical benzyl benzoate (BB) for treating scabies in a community setting. **METHODS:** The trial included patients aged 5-65 years with scabies who attended the dermatology department at the Institut d'Hygiène Sociale in Dakar, Senegal. **The randomized, open trial considered three treatments: a single application of 12.5% BB over 24 hours (BB1 group), two applications of BB, each over 24 hours (BB2 group), and oral IV, 150-200 microg/kg (IV group).** The primary endpoint was the disappearance of skin lesions and itching at day 14. If necessary, treatment was repeated and patients were evaluated until cured. Results were analysed on an intention-to-treat basis. A pre-planned intermediate analysis was carried out after the BB1, BB2 and IV groups had recruited 68, 48 and 65 patients, respectively. **FINDINGS: At day 14, 33 patients (68.8%) in the BB2 group were cured versus 37 (54.4%) in the BB1 group and 16 (24.6%) in the IV group (P < 10⁻⁶). Bacterial superinfection occurred more often in the IV group than in the BB1 and BB2 groups combined (28% versus 7.8%, respectively; P = 0.006). At day 28, 46 patients (95.8%) in the BB2 group were cured versus 52 (76.5%) in the BB1 group and 28 (43.1%) in the IV group (P < 10⁻⁵). These clear findings prompted early study cessation.** **CONCLUSION:** Topical BB was clearly more effective than oral IV for treating scabies in a Senegalese community.

Surgical problems

Lancet. 2010 Feb 20;375(9715):664-72. Epub 2010 Feb 3.

Antimicrobial treatment for early, limited *Mycobacterium ulcerans* infection: a randomised controlled trial.

Nienhuis WA, Stienstra Y, Thompson WA, Awuah PC, Abass KM, Tuah W, Awua-Boateng NY, Ampadu EO, Siegmund V, Schouten JP, Adjei O, Bretzel G, van der Werf TS.

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Abstract

BACKGROUND: Surgical debridement was the standard treatment for *Mycobacterium ulcerans* infection (Buruli ulcer disease) until WHO issued provisional guidelines in 2004 recommending treatment with antimicrobial drugs (streptomycin and rifampicin) in addition to surgery. These recommendations were based on observational studies and a small pilot study with microbiological endpoints. We investigated the efficacy of two regimens of antimicrobial treatment in early-stage *M ulcerans* infection. **METHODS:** In this parallel, open-label, randomised trial undertaken in two sites in Ghana, patients were eligible for enrolment if they were aged 5 years or older and had early (duration <6 months), limited (cross-sectional diameter <10 cm), *M ulcerans* infection confirmed by dry-reagent-based PCR. **Eligible patients were randomly assigned to receive intramuscular streptomycin (15 mg/kg once daily) and oral rifampicin (10 mg/kg once daily) for 8 weeks (8-week streptomycin group; n=76) or streptomycin and rifampicin for 4 weeks followed by rifampicin and clarithromycin (7.5 mg/kg once daily), both orally, for 4 weeks (4-week streptomycin plus 4-week clarithromycin group; n=75).** Randomisation was done by computer-generated minimisation for study site and type of lesion (ulceration or no ulceration). The randomly assigned allocation was sent from a central site by cell-phone text message to the study coordinator. The primary endpoint was lesion healing at 1 year after the start of treatment without lesion recurrence or extensive surgical debridement. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00321178. **FINDINGS:** Four patients were lost to follow-up (8-week streptomycin, one; 4-week streptomycin plus 4-week clarithromycin, three). **Since these four participants had healed lesions at their last assessment, they were included in the analysis for the primary endpoint. 73 (96%) participants in the 8-week streptomycin group and 68 (91%) in the 4-week streptomycin plus 4-week clarithromycin group had healed lesions at 1 year (odds ratio 2.49, 95% CI 0.66 to infinity; p=0.16, one-sided Fisher's exact test).** No participants had lesion recurrence at 1 year. Three participants had vestibulotoxic events (8-week streptomycin, one; 4-week streptomycin plus 4-week clarithromycin, two). One participant developed an injection abscess and two participants developed an abscess close to the initial lesion, which was incised and drained (all three participants were in the 4-week streptomycin plus 4-week clarithromycin group). **INTERPRETATION: Antimycobacterial treatment for *M ulcerans* infection is effective in early, limited disease. 4 weeks of streptomycin and rifampicin followed by 4 weeks of rifampicin and clarithromycin has similar efficacy to 8 weeks of streptomycin and rifampicin; however, the number of injections of streptomycin can be reduced by switching to oral clarithromycin after 4 weeks.**

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Pediatr Surg Int. 2009 Dec;25(12):1113-5. Epub 2009 Sep 1.

Role of alpha adrenergic blocker in the management of posterior urethral valves.

Abraham MK, Nasir AR, Sudarsanan B, Puzhankara R, Kedari PM, Unnithan GR, Damisetti KR, Narayanan T.

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Abstract

PURPOSE: To evaluate the effect of Terazosin (alpha1 adrenergic blocker) on bladder emptying in children with posterior urethral valves. **MATERIALS AND METHODS:** Forty-two children with significant post void residual urine after valves ablation were placed on Terazosin ranging from 0.25 to 2 mg. Post void urine at the commencement and at follow up was monitored with abdominal ultrasound. **RESULTS:** Post void residual urine significantly reduced in 40 patients (95%) who were put on Terazosin. Mean pretreatment PVR was 15.7 ml and mean PVR at the last follow up was 2.4 ml ($P = 0.000$). This was a reduction of 85% in the pretreatment post void residual urine volume. All the patients had improvement in urinary stream. One patient reacted to Terazosin with hypotension necessitating its withdrawal. Mean follow up was 17 months. **CONCLUSION: Terazosin has proved to be safe and results in significant improvement in bladder emptying in our patients with posterior urethral valves.** Randomized controlled trial and long-term follow up are necessary to further define the role of alpha1 adrenergic blocker therapy in children with posterior urethral valves. This study will become the justification for such a study.

Tuberculosis

Indian Pediatr. 2010 Jan 7;47(1):67-73. Epub 2009 May 20.

<http://www.indianpediatrics.net/jan2010/67.pdf>

Intermittent or daily short course chemotherapy for tuberculosis in children: meta-analysis of randomized controlled trials.

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Abstract

OBJECTIVE: To compare the effectiveness of intermittent with daily chemotherapy (both containing rifampicin) in childhood tuberculosis (age 16yrs) in achieving cure significant improvement. **DESIGN:** Systematic Review and Meta-analysis. **METHODS:** MEDLINE and the Cochrane Library were searched for randomized trials of antitubercular regimens containing rifampicin, in children 16 yrs or less with tuberculosis. Two reviewers independently assessed trial eligibility and quality. Data from full articles of selected studies were independently extracted by two authors and analyzed. The odds ratio was obtained for the pooled data in two groups (intermittent and daily therapy). **OUTCOME VARIABLES:** Cure/significant

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improvement, relapse rate and adverse events. RESULTS: Four randomized controlled trials comparing twice weekly and daily therapy including 466 children (pulmonary 439; extrapulmonary 27) met the inclusion criteria. Baseline data were comparable. On quality assessment, 3 studies scored 2 and one study scored 3 out of 5 points. **Per protocol analysis showed that children receiving intermittent regimen were less likely to be cured than those receiving daily therapy (OR 0.27; 95% CI: 0.14, 0.51). The results of intention to treat analysis suggest similar trend towards lower cure rates with twice weekly regimen (OR 0.66; 95% CI: 0.23-1.84).** CONCLUSION: Twice weekly intermittent short course therapy is less likely to cure tuberculosis in children as compared to daily therapy. There is a need for better quality randomized controlled trials for assessing efficacy of alternate schedule for intermittent therapy for childhood tuberculosis.

BMC Med. 2009 Nov 3;7:67.

<http://www.biomedcentral.com/1741-7015/7/67>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2777189/?tool=pubmed>

Adherence to isoniazid prophylaxis among HIV-infected children: a randomized controlled trial comparing two dosing schedules.

le Roux SM, Cotton MF, Golub JE, le Roux DM, Workman L, Zar HJ.

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Abstract

BACKGROUND: Tuberculosis contributes significantly to morbidity and mortality among HIV-infected children in sub-Saharan Africa. Isoniazid prophylaxis can reduce tuberculosis incidence in this population. However, for the treatment to be effective, adherence to the medication must be optimized. We investigated adherence to isoniazid prophylaxis administered daily, compared to three times a week, and predictors of adherence amongst HIV-infected children. **METHODS:** **We investigated adherence to study medication in a two centre, randomized trial comparing daily to three times a week dosing of isoniazid.** The study was conducted at two tertiary paediatric care centres in Cape Town, South Africa. Over a 5 year period, we followed 324 HIV-infected children aged \geq 8 weeks. **Adherence information based on pill counts was available for 276 children.** Percentage adherence was calculated by counting the number of pills returned. Adherence \geq 90% was considered to be optimal. Analysis was done using summary and repeated measures, comparing adherence to the two dosing schedules. Mean percentage adherence (per child during follow-up time) was used to compare the mean of each group as well as the proportion of children achieving an adherence of \geq 90% in each group. For repeated measures, percentage adherence (per child per visit) was dichotomized at 90%. A logistic regression model with generalized estimating equations, to account for within-individual correlation, was used to evaluate the impact of the dosing schedule. Adjustments were made for potential confounders and we assessed potential baseline and time-varying adherence determinants. **RESULTS:** **The overall adherence to isoniazid was excellent, with a mean adherence of 94.7% (95% confidence interval [CI] 93.5-95.9);**

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similar mean adherence was achieved by the group taking daily medication (93.8%; 95% CI 92.1-95.6) and by the three times a week group (95.5%; 95% CI 93.8-97.2). Two-hundred and seventeen (78.6%) children achieved a mean adherence of $\geq 90\%$. Adherence was similar for daily and three times a week dosing schedules in univariate (odds ratio [OR] 0.88; 95% CI 0.66-1.17; $P = 0.38$) and multivariate (adjusted OR 0.85; 95% CI 0.64-1.11; $P = 0.23$) models. **Children from overcrowded homes were less adherent (adjusted OR 0.71; 95% CI 0.54-0.95; $P = 0.02$).** Age at study visit was predictive of adherence, with better adherence achieved in children older than 4 years (adjusted OR 1.96; 95% CI 1.16-3.32; $P = 0.01$). **CONCLUSION:** Adherence to isoniazid was excellent regardless of the dosing schedule used. Intermittent dosing of isoniazid prophylaxis can be considered as an alternative to daily dosing, without compromising adherence or efficacy.

Vaccines and immunization

Immunization coverage

BMJ. 2010 May 17;340:c2220. doi: 10.1136/bmj.c2220.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2871989/?tool=pubmed>

Improving immunisation coverage in rural India: clustered randomised controlled evaluation of immunisation campaigns with and without incentives.

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Abstract

OBJECTIVE: To assess the efficacy of modest non-financial incentives on immunisation rates in children aged 1-3 and to compare it with the effect of only improving the reliability of the supply of services. **DESIGN:** Clustered randomised controlled study. **SETTING:** Rural Rajasthan, India. **PARTICIPANTS:** 1640 children aged 1-3 at end point. **INTERVENTIONS:** 134 villages were randomised to one of three groups: a once monthly reliable immunisation camp (intervention A; 379 children from 30 villages); a once monthly reliable immunisation camp with small incentives (raw lentils and metal plates for completed immunisation; intervention B; 382 children from 30 villages), or control (no intervention, 860 children in 74 villages). Surveys were undertaken in randomly selected households at baseline and about 18 months after the interventions started (end point). **MAIN OUTCOME MEASURES:** Proportion of children aged 1-3 at the end point who were partially or fully immunised. **RESULTS:** Among children aged 1-3 in the end point survey, rates of full immunisation were 39% (148/382, 95% confidence interval 30% to 47%) for intervention B villages (reliable immunisation with incentives), 18% (68/379, 11% to 23%) for intervention A villages (reliable immunisation without incentives), and 6% (50/860, 3% to 9%) for control villages. The relative risk of complete immunisation for intervention B versus control was 6.7 (4.5 to 8.8) and for

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intervention B versus intervention A was 2.2 (1.5 to 2.8). Children in areas neighbouring intervention B villages were also more likely to be fully immunised than those from areas neighbouring intervention A villages (1.9, 1.1 to 2.8). The average cost per immunisation was \$28 (1102 rupees, about pound16 or euro19) in intervention A and \$56 (2202 rupees) in intervention B. CONCLUSIONS: Improving reliability of services improves immunisation rates, but the effect remains modest. Small incentives have large positive impacts on the uptake of immunisation services in resource poor areas and are more cost effective than purely improving supply. TRIAL REGISTRATION: IRISCTN87759937.

Trop Med Int Health. 2010 Jan;15(1):140-7. Epub 2009 Nov 17.

<http://www3.interscience.wiley.com/journal/122686868/abstract>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858790/?tool=pubmed>

Determinants of third dose of diphtheria-tetanus-pertussis (DTP) completion among children who received DTP1 at rural immunization centres in Pakistan: a cohort study.

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Abstract

OBJECTIVE: In Pakistan, a high proportion of children fail to complete third dose of diphtheria-tetanus-pertussis (DTP3) after having received the first dose (DTP1). A cohort study was conducted to identify the factors predicting three doses of diphtheria-tetanus-pertussis (DTP3) completion among children who have received DTP1 at six centres of Expanded Programme on Immunization (EPI) in rural Pakistan. **METHOD:** We analyzed a cohort of mother-child pairs enrolled at DTP1 between November 2005 and May 2006 in the standard care group of a larger randomized controlled trial. Data were collected from mothers on a structured questionnaire at enrollment, and each child was followed up at clinic visits for 90 days to record dates of DTP2 and DTP3. Multivariable log-binomial regression analysis was performed to identify the independent predictors of DTP3 completion. **RESULTS:** Only 39% (149/378) of enrolled children completed DTP3 during the follow-up period. After adjusting for the centre of enrollment in multivariable analysis, **DTP3 completion was higher among children who were < or =60 days old at enrolment [adjusted risk ratio (Adj. RR) 1.39, 95% confidence interval (CI): 1.06-1.82], who were living in a household with monthly household income >Rs. 3000 (US\$ 50) (Adj. RR 1.76, 95% CI: 1.16-2.65), and who were living < or =10 min away from EPI centre (Adj. RR 1.31, 95% CI: 1.04-1.66).** **CONCLUSIONS:** Interventions targeting childhood immunization dropouts should focus on bringing more children to EPI centres on-time for initial immunization. Relocation of existing EPI centres and creation of new EPI centres at appropriate locations may decrease the travel time to the EPI centres and result in fewer immunization dropouts.

BCG vaccine

BMJ. 2010 Mar 15;340:c671. doi: 10.1136/bmj.c671.

http://www.bmj.com/cgi/content/full/340/mar15_1/c671?view=long&pmid=20231251

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2839082/?tool=pubmed>

Effect of revaccination with BCG in early childhood on mortality: randomised trial in Guinea-Bissau.

Roth AE, Benn CS, Ravn H, Rodrigues A, Lisse IM, Yazdanbakhsh M, Whittle H, Aaby P.

Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau.

Abstract

OBJECTIVE: To determine whether BCG revaccination at 19 months of age reduces overall child mortality. **DESIGN:** Randomised trial, with follow-up to age 5. **SETTING:** A health project in Bissau, Guinea-Bissau, which maintains a health and demographic surveillance system in an urban area with 90 000 inhabitants. **PARTICIPANTS:** 2871 children aged 19 months to 5 years with low or no reactivity to tuberculin and who were not severely sick on the day of enrollment. **INTERVENTION:** BCG vaccination or no vaccination (control). **MAIN OUTCOME MEASURE:** Hazard ratios for mortality. **RESULTS:** 77 children died during follow-up. Compared with controls, the BCG revaccinated children had a hazard ratio of 1.20 (95% confidence interval 0.77 to 1.89). Two hundred and fifty children were admitted to hospital for the first time between enrollment and the end of the study, with an incidence rate ratio for BCG revaccinated children versus controls of 1.04 (0.81 to 1.33). **The trial was stopped prematurely because of a cluster of deaths in the BCG arm of the study. This increase in mortality occurred at a time when many children had received missing vaccinations or vitamin A or iron supplementation; the hazard ratio for BCG revaccinated children compared with controls was 2.69 (1.05 to 6.88) in the period after these campaigns. Throughout the trial, the effect of BCG revaccination on mortality was significantly different (P=0.006) in children who had received diphtheria-tetanus-pertussis (DTP) booster vaccination before enrollment (hazard ratio 0.36, 0.13 to 0.99) and children who had not received the booster before enrollment (1.78, 1.04 to 3.04).** **CONCLUSIONS:** There was no overall beneficial effect of being revaccinated with BCG. The effect of BCG revaccination on mortality might depend on other health interventions.

Vaccine. 2009 Sep 4;27(40):5488-95. Epub 2009 Jul 17.

Delaying BCG vaccination from birth to 10 weeks of age may result in an enhanced memory CD4 T cell response.

Kagina BM, Abel B, Bowmaker M, Scriba TJ, Gelderbloem S, Smit E, Erasmus M, Nene N, Walzl G, Black G, Hussey GD, Hesselning AC, Hanekom WA.

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South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Diseases and Molecular Medicine and School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.

Abstract

BACKGROUND: In most tuberculosis (TB) endemic countries, bacillus Calmette-Guérin (BCG) is usually given around birth to prevent severe TB in infants. The neonatal immune system is immature. Our hypothesis was that delaying BCG vaccination from birth to 10 weeks of age would enhance the vaccine-induced immune response. **METHODS:** **In a randomized clinical trial, BCG was administered intradermally either at birth (n=25) or at 10 weeks of age (n=21). Ten weeks after vaccination, and at 1 year of age, vaccine-specific CD4 and CD8 T cell responses were measured with a whole blood intracellular cytokine assay.** **RESULTS:** **Infants who received delayed BCG vaccination demonstrated higher frequencies of BCG-specific CD4 T cells, particularly polyfunctional T cells co-expressing IFN-gamma, TNF-alpha and IL-2, and most strikingly at 1 year of age.** **CONCLUSIONS:** Delaying BCG vaccination from birth to 10 weeks of age enhances the quantitative and qualitative BCG-specific T cell response, when measured at 1 year of age.

Hepatitis B vaccine

Vaccine. 2010 Apr 30;28(20):3595-601. Epub 2010 Feb 26.

Immunogenicity and safety of a novel yeast *Hansenula polymorpha*-derived recombinant Hepatitis B candidate vaccine in healthy adolescents and adults aged 10-45 years.

Tregnaghi MW, Voelker R, Santos-Lima E, Zambrano B.

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miguel@millicom.com.ar

Abstract

The aim was to determine whether the immunogenicity of an investigational hepatitis B vaccine (spHB) is at least as high as that of a licensed control vaccine, Engerix B, and to evaluate its safety before inclusion in new pediatric combination vaccines. Two randomized, controlled, blind-observer, Phase 3 trials were performed: one in Argentina (344 participants aged 10-15 years, 10 microg HBsAg/dose) and one in Uruguay (344 participants aged 16-45 years, 20 microg HBsAg/dose). Both vaccines were given in a 0, 1, 6 month schedule to all participants with a baseline anti-Hep B antibody titer <0.6 mIU/mL. Antibody titers were measured pre-dose 1, 1 month after dose 2, pre-dose 3, and 1 month after dose 3. Statistical non-inferiority analyses were performed on seroprotection rates (SP) post-dose 3 (% with anti-Hep B titers ≥ 10 mIU/mL; delta non-inferiority limit of -10%). In both studies, SP for the spHB vaccine was 100% and the spHB vaccine was non-inferior in terms of SP to the licensed control vaccine. GMTs post-dose 3 were approximately 1.8- and 4.1-fold higher for spHB in the 10-15 year and 16-45 year age groups, respectively. Reactogenicity was low for each vaccine, after each dose.

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This highly immunogenic hepatitis B candidate vaccine was selected for further investigation as a component of new pediatric combination vaccines.

Shigella vaccine

Vaccine. 2010 Mar 2;28(10):2231-5. Epub 2010 Jan 5.

Age-related efficacy of Shigella O-specific polysaccharide conjugates in 1-4-year-old Israeli children.

Passwell JH, Ashkenzi S, Banet-Levi Y, Ramon-Saraf R, Farzam N, Lerner-Geva L, Even-Nir H, Yerushalmi B, Chu C, Shiloach J, Robbins JB, Schneerson R; Israeli Shigella Study Group.

Kalmus Y, Garberg I, Tirosch N, Alter E, Gutratz A, Shalev H, Krinawi R, el Krinawi S, Chamny S, Huri N, Lotem Y, Shirer E, Poznansky O, Yechieli R, Fradkin A, Arbiv L, Keisar I, Korman H, Buchnik H, Abumoch J, Walid A, Abu-Husain H, Najjar R, Ghrayeb G, Altman V, Rohana R, Halabi K, Askin Y, Kristal H, Ya'acobi J, Rogani S, Ezer Y, Amar S, Miron D, Marei A, Gebara D, Berkun Y, Siman-Tov M, Beit-Or A, Meir I, Pinco E, Taran D, Zvieli S, Biton M, Siman-Tov C, Keller N, Smollan G, Melamed E, Vasilev V, Japheth R, Boyko V.

Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 52621, Israel.

Abstract

BACKGROUND: Despite its high worldwide morbidity and mortality, there is yet no licensed vaccine for shigellosis. We reported the safety and immunogenicity of Shigella O-specific polysaccharide-protein conjugates in adults and young children and efficacy of Shigella sonnei conjugate in young adults. **METHODS: A double-blinded, randomized and vaccine-controlled Phase 3 evaluation of S. sonnei and Shigella flexneri 2a O-SP-rEPA conjugates, 25 microg, injected IM twice, 6 weeks apart, into healthy 1-4 years old, is reported.** The children were followed for 2 years by telephone every other week and stool cultures were obtained for each episode of acute diarrhea (> or =3 loose stools/day or a bloody/mucous stool). Sera were taken randomly from 10% of the participants for IgG anti-LPS and anti-carrier levels. **RESULTS:** Of the 2799 enrollees, 1433 received S. sonnei and 1366 S. flexneri 2a conjugates; 2699 (96.4%) completed the 2-year follow-up. Local reactions occurred in approximately 5% and approximately 4% had temperatures > or =38.0 degrees C lasting 1-2 days. There were no serious adverse events attributable to the vaccines. Of the 3295 stool cultures obtained, 125 yielded S. sonnei and 21 S. flexneri 2a. Immunogenicity and efficacy were age-related. **The overall efficacy of the S. sonnei conjugate was 27.5%; 71.1% (P=0.043) in the 3-4 years old.** The numbers for S. flexneri 2a were too few for meaningful analysis. Cross-protection by S. flexneri 2a for non-vaccine S. flexneri types was found, but the numbers were too few for statistical significance. There was an age-related rise of vaccine-specific IgG anti-LPS in both groups, peaking at about 10 weeks and declining thereafter, but remaining > or =4-fold higher than in the controls 2 years after the second dose. **CONCLUSIONS:** Shigella conjugates are safe and immunogenic in 1-4 years old. The S. sonnei conjugate elicited 71.1% efficacy in the 3-4 years old and can be predicted to be efficacious in individuals older than 3 years of age. These results urge studies with our improved conjugates.

Typhoid vaccine

N Engl J Med. 2009 Jul 23;361(4):335-44.

<http://content.nejm.org/cgi/content/abstract/361/4/335>

A cluster-randomized effectiveness trial of Vi typhoid vaccine in India.

Sur D, Ochiai RL, Bhattacharya SK, Ganguly NK, Ali M, Manna B, Dutta S, Donner A, Kanungo S, Park JK, Puri MK, Kim DR, Dutta D, Bhaduri B, Acosta CJ, Clemens JD.

National Institute of Cholera and Enteric Diseases, Kolkata, India.

Abstract

BACKGROUND: Typhoid fever remains an important cause of illness and death in the developing world. Uncertainties about the protective effect of Vi polysaccharide vaccine in children under the age of 5 years and about the vaccine's effect under programmatic conditions have inhibited its use in developing countries. **METHODS:** We conducted a phase 4 effectiveness trial in which slum-dwelling residents of Kolkata, India, who were 2 years of age or older were randomly assigned to receive a single dose of either Vi vaccine or inactivated hepatitis A vaccine, according to geographic clusters, with 40 clusters in each study group. The subjects were then followed for 2 years. **RESULTS:** A total of 37,673 subjects received a dose of a study vaccine. The mean rate of vaccine coverage was 61% for the Vi vaccine clusters and 60% for the hepatitis A vaccine clusters. Typhoid fever was diagnosed in 96 subjects in the hepatitis A vaccine group, as compared with 34 in the Vi vaccine group, with no subject having more than one episode. **The level of protective effectiveness for the Vi vaccine was 61% (95% confidence interval [CI], 41 to 75; P<0.001 for the comparison with the hepatitis A vaccine group). Children who were vaccinated between the ages of 2 and 5 years had a level of protection of 80% (95% CI, 53 to 91).** Among unvaccinated members of the Vi vaccine clusters, the level of protection was 44% (95% CI, 2 to 69). The overall level of protection among all residents of Vi vaccine clusters was 57% (95% CI, 37 to 71). No serious adverse events that were attributed to either vaccine were observed during the month after vaccination. **CONCLUSIONS: The Vi vaccine was effective in young children and protected unvaccinated neighbors of Vi vaccinees.** The potential for combined direct and indirect protection by Vi vaccine should be considered in future deliberations about introducing this vaccine in areas where typhoid fever is endemic.

Rotavirus vaccine

N Engl J Med. 2010 Jan 28;362(4):289-98.

<http://content.nejm.org/cgi/content/abstract/362/4/289>

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Effect of human rotavirus vaccine on severe diarrhea in African infants.

Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, Ngwira B, Victor JC, Gillard PH, Cheuvart BB, Han HH, Neuzil KM.

Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Johannesburg, South Africa.

Abstract

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 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.**

Cholera vaccine

Lancet. 2009 Nov 14;374(9702):1694-702. Epub 2009 Oct 8.

Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial.

Sur D, Lopez AL, Kanungo S, Paisley A, Manna B, Ali M, Niyogi SK, Park JK, Sarkar B, Puri MK, Kim DR, Deen JL, Holmgren J, Carbis R, Rao R, Nguyen TV, Donner A, Ganguly NK, Nair GB, Bhattacharya SK, Clemens JD.

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National Institute of Cholera and Enteric Diseases, Kolkata, India.

BACKGROUND: Oral cholera vaccines consisting of killed whole cells have been available for many years, but they have not been used extensively in populations with endemic disease. An inexpensive, locally produced oral killed-whole-cell vaccine has been used in high-risk areas in Vietnam. To expand the use of this vaccine, it was modified to comply with WHO standards. We assessed the efficacy and safety of this modified vaccine in a population with endemic cholera. **METHODS:** In this double-blind trial, 107 774 non-pregnant residents of Kolkata, India, aged 1 year or older, were cluster-randomised by dwelling to receive two doses of either modified killed-whole-cell cholera vaccine (n=52 212; 1966 clusters) or heat-killed *Escherichia coli* K12 placebo (n=55 562; 1967 clusters), both delivered orally. Randomisation was done by computer-generated sequence in blocks of four. The primary endpoint was prevention of episodes of culture-confirmed *Vibrio cholerae* O1 diarrhoea severe enough for the patient to seek treatment in a health-care facility. We undertook an interim, per-protocol analysis at 2 years of follow-up that included individuals who received two completely ingested doses of vaccine or placebo. We assessed first episodes of cholera that occurred between 14 days and 730 days after receipt of the second dose. This study is registered with ClinicalTrials.gov, number NCT00289224. **FINDINGS:** 31 932 participants assigned to vaccine (1721 clusters) and 34 968 assigned to placebo (1757 clusters) received two doses of study treatment. **There were 20 episodes of cholera in the vaccine group and 68 episodes in the placebo group (protective efficacy 67%; one-tailed 99% CI, lower bound 35%, p<0.0001). The vaccine protected individuals in age-groups 1.0-4.9 years, 5.0-14.9 years, and 15 years and older, and protective efficacy did not differ significantly between age-groups (p=0.28).** We recorded no vaccine-related serious adverse events. **INTERPRETATION:** This modified killed-whole-cell oral vaccine, compliant with WHO standards, is safe, provides protection against clinically significant cholera in an endemic setting, and can be used in children aged 1.0-4.9 years, who are at highest risk of developing cholera in endemic settings.

Vaccine. 2009 Dec 11;28(2):422-9. Epub 2009 Oct 17.

CD4+ T-cell responses to an oral inactivated cholera vaccine in young children in a cholera endemic country and the enhancing effect of zinc supplementation.

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International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh.

Abstract

Immunization of young children with the oral inactivated whole cell cholera vaccine Dukoral((R)) containing recombinant cholera toxin B subunit (CTB) induces antibody responses which can be further enhanced by zinc supplementation. **We have investigated if immunization with the cholera vaccine induces specific T-cell responses in young children and also whether zinc supplementation influences these responses.** Bangladeshi children (10-18 months old) received vaccine alone, vaccine together with zinc supplementation or only zinc. T-cell blast formation indicating a proliferative response was analyzed by the flow

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cytometric assay of cell-mediated immune response in activated whole blood (FASCIA) and cytokines were measured by ELISA. Stronger T-cell responses were detected if a modified CTB molecule (mCTB) with reduced binding to GM1 ganglioside was used for cell stimulation compared to normal CTB. After vaccination, CD4+ T cells responded to mCTB with significantly increased blast formation ($P<0.01$) and IFN-gamma production ($P<0.05$) compared to before vaccination. No responses to mCTB were detected in children receiving zinc alone ($P>0.05$). The IFN-gamma production was significantly higher ($P<0.01$) but the blast formation comparable ($P>0.05$) in children receiving zinc plus vaccine compared to in children receiving vaccine alone. The vibriocidal antibody responses induced by the vaccine were also significantly higher in children receiving zinc supplementation ($P<0.001$). **Our results thus show that oral cholera vaccination induces a Th1 T-cell response in young children, and that the IFN-gamma as well as the vibriocidal antibody responses can be enhanced by zinc supplementation.**

Vaccine. 2009 Nov 16;27(49):6887-93. Epub 2009 Sep 15.

Immune responses following one and two doses of the reformulated, bivalent, killed, whole-cell, oral cholera vaccine among adults and children in Kolkata, India: a randomized, placebo-controlled trial.

Kanungo S, Paisley A, Lopez AL, Bhattacharya M, Manna B, Kim DR, Han SH, Attridge S, Carbis R, Rao R, Holmgren J, Clemens JD, Sur D.

National Institute of Cholera and Enteric Diseases, Kolkata, India.

Abstract

Immune responses after one and two doses of the reformulated killed oral cholera vaccine were measured in a double-blind, randomized, placebo-controlled trial of 77 adults aged 18-40 years and 77 children aged 1-17 years residing in Kolkata, India. 65% of adults and 87% of children and 46% of adults and 82% of children exhibited a $>$ or $=4$ -fold rise in serum *Vibrio cholerae* O1 vibriocidal antibody titers from baseline following dose 1 and 2, respectively. Responses to *V. cholerae* O139 were less pronounced but followed a similar pattern. We demonstrate that in a cholera-endemic area, the vaccine elicited vibriocidal responses after a single-dose of the vaccine.

Rabies vaccine

Vaccine. 2009 Dec 10;28(1):148-51. Epub 2009 Oct 8.

A comparative study on the safety and immunogenicity of Purified duck embryo vaccine [corrected] (PDEV, Vaxirab) with purified chick embryo cell vaccine (PCEC, Rabipur) and purified vero cell rabies vaccine (PVRV, Verorab).

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Ashwathnarayana DH, Madhusudana SN, Sampath G, Sathpathy DM, Mankeshwar R, Ravish HH, Ullas PT, Behra TR, Sudarshan MK, Gangaboraiah, Shamanna M.

Dept. of Community Medicine, Kempegowda Institute of Medical Sciences, Bangalore 560004, India.

Abstract

Rabies is a fatal but preventable disease. Cell culture vaccines (CCV) and purified duck embryo vaccines (PDEV) are currently recommended by WHO for post-exposure prophylaxis. In India, a PDEV (Vaxirab) is being manufactured and is in use since 2003. In the present study, we have evaluated the safety, immunogenicity and tolerance of this vaccine with two other WHO approved CCVs, viz., purified chick embryo cell vaccine (PCEC, Rabipur) and purified vero cell rabies vaccine (PVRV, Verorab). This study was an open label, randomized phase IV comparative clinical trial. **A total of 152 people bitten by dogs and other animals were recruited from 4 different centres from India. They were randomly assigned to receive one of the vaccines by Essen intramuscular regimen (52 subjects received Vaxirab and 50 each Rabipur and Verorab) and rabies immunoglobulin was also administered in all category III exposures.** Their blood samples were collected on day 0 (prior to vaccination), 14, 28, 90 and 180. Side effects if any were monitored. The rabies neutralizing antibody titers in their blood samples were estimated by the rapid fluorescent focus inhibition test (RFFIT). **Subjects in all three groups had neutralizing antibody titers by day 14 (>0.5 IU/mL) and geometric mean titers (GMT) observed for different vaccines on all days tested did not vary significantly ($p>0.5$).** Side effects observed were minimal and did not vary significantly among the groups. The results of the present study indicate that PDEV (Vaxirab) is as safe, tolerable and immunogenic as both PCEC (Rabipur) and PVRV (Verorab). Thus this vaccine can be a good alternative to WHO approved CCVs for rabies post-exposure prophylaxis.

Zhongguo Ji Hua Mian Yi. 2009 Oct;15(5):447-50.

[Safety and immunogenicity of rabies vaccine (chick embryo cell) for human use produced in Germany and India]

Zhu FC, Wu CH, Meng FY.

Jiangsu Provincial Center for Disease Control and Prevention, Nanjing 210009, Jiangsu, China.

Abstract

OBJECTIVE: To evaluate the safety and immunogenicity of Rabipur produced in India. **METHODS:** A random and single-blind study was conducted to compare the safety, effect and sero conversion rates. Rabipur produced in Germany used as control group. **RESULTS:** The results showed that they were no severe systemic and local reaction occurred in trial group (Rabipur produced in India). The difference between trial group and control group was not significant. 14 day and 45 days after the first dose, the seroconversion rates of the two groups were 100%. 14 day and 45 days after the first dose, GMC of the two groups increased obviously and highly beyond 0.5TU/ml. **CONCLUSION:** Rabipur produced in India has excellent safety and immunogenicity.

Influenza vaccine

Lancet. 2010 Jan 2;375(9708):56-66. Epub 2009 Dec 15.

Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial.

Liang XF, Wang HQ, Wang JZ, Fang HH, Wu J, Zhu FC, Li RC, Xia SL, Zhao YL, Li FJ, Yan SH, Yin WD, An K, Feng DJ, Cui XL, Qi FC, Ju CJ, Zhang YH, Guo ZJ, Chen PY, Chen Z, Yan KM, Wang Y.

Chinese Center for Disease Control and Prevention, Beijing, China.

Abstract

BACKGROUND: The current influenza pandemic calls for a safe and effective vaccine. We assessed the safety and immunogenicity of eight formulations of 2009 pandemic influenza A H1N1 vaccine produced by ten Chinese manufacturers. **METHODS:** In this multicentre, double-blind, randomised trial, 12 691 people aged 3 years or older were recruited in ten centres in China. In each centre, participants were stratified by age and randomly assigned by a random number table to receive one of several vaccine formulations or placebo. The study assessed eight formulations: split-virion formulation containing 7.5 microg, 15 microg, or 30 microg haemagglutinin per dose, with or without aluminium hydroxide adjuvant, and whole-virion formulation containing 5 microg or 10 microg haemagglutinin per dose, with adjuvant. All formulations were produced from the reassortant strain X-179A (A/California/07/2009-A/PR/8/34). We analysed the safety (adverse events), immunogenicity (geometric mean titre [GMT] of haemagglutination inhibition antibody), and seroprotection (GMT \geq 1:40) of the formulations. Analysis was by per protocol. Two sites registered their trial with ClinicalTrials.gov, numbers NCT00956111 and NCT00975572. The other eight studies were registered with the State Food and Drug Administration of China. **FINDINGS:** 12 691 participants received the first dose on day 0, and 12 348 participants received the second dose on day 21. **The seroprotection rate 21 days after the first dose of vaccine ranged from 69.5% (95% CI 65.9-72.8) for the 7.5 microg adjuvant split-virion formulation to 92.8% (91.9-93.6) for the 30 microg non-adjuvant split-virion formulation.** The seroprotection rate was 86.5% (796 of 920; 84.1-88.7) in recipients of one dose of the 7.5 microg non-adjuvant split-virion vaccine compared with 9.8% (140 of 1432; 8.3-11.4) in recipients of placebo ($p < 0.0001$). **One dose of the 7.5 microg non-adjuvant split-virion vaccine induced seroprotection in 178 of 232 children (aged 3 years to <12 years; 76.7%, 70.7-82.0), 211 of 218 adolescents (12 years to <18 years; 96.8%, 93.5-98.7), 289 of 323 adults (18-60 years; 89.5%, 85.6-92.6), and 118 of 147 adults older than 60 years (80.3%, 72.9-86.4), meeting the European Union's licensure criteria for seroprotection in all age-groups. In children, a second dose of the 7.5 microg formulation increased the seroprotection rate to 97.7% (215 of 220, 94.8-99.3).** Adverse reactions were mostly mild or moderate, and self-limited. Severe adverse effects occurred in 69 (0.6%, 0.5-0.8) recipients of vaccine compared with one recipient (0.1%, 0-0.2) of placebo. **The most common severe adverse reaction was fever, which occurred in 25 (0.22%; 0.14-0.33) recipients of vaccine after the first dose and four (0.04%; 0.01-0.09) recipients of vaccine after the second dose compared with no recipients of placebo after either dose.** **INTERPRETATION:** One dose of non-adjuvant split-virion vaccine containing 7.5 microg haemagglutinin could be promoted as the formulation of choice against 2009 pandemic influenza A H1N1 for people aged 12 years or older. In children (aged <12 years), two 7.5 mug doses might be needed.

Vaccine. 2009 Sep 4;27(40):5472-9. Epub 2009 Jul 17.

A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children.

Breiman RF, Brooks WA, Goswami D, Lagos R, Borja-Tabora C, Lanata CF, Londoño JA, Lum LC, Rappaport R, Razmpour A, Walker RE, Gruber WC, Forrest BD.

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Abstract

Live attenuated influenza vaccine (LAIV) provides a useful tool to rapidly immunize populations in the developing world to prevent influenza outbreaks. In this noninferiority trial conducted in Asia and South America, where oral poliovirus vaccine (OPV) is still used, 2503 children aged 6 to <36 months with three polio immunizations were randomized to receive LAIV+OPV, placebo+OPV, or LAIV only. Immune responses in children receiving concomitant LAIV+OPV were noninferior to those observed in recipients of either vaccine alone. Response rates for different poliovirus types were similar in recipients of LAIV+OPV and placebo+OPV. Response rates to all influenza strains were similar in LAIV+OPV and LAIV-only recipients. Concomitant OPV and LAIV were safely administered to young children.

Vitamin A

(See also Maternal health, nutrition and micronutrient supplementation)

Am J Clin Nutr. 2009 Sep;90(3):629-39. Epub 2009 Jul 29.

Does vitamin A supplementation interact with routine vaccinations? An analysis of the Ghana Vitamin A Supplementation Trial.

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Abstract

BACKGROUND: The World Health Organization recommends vitamin A supplementation (VAS) at vaccination contacts after 6 mo of age to reduce mortality. However, it is unknown whether the effect of VAS is independent of vaccinations. One of the original VAS trials from Ghana had collected vaccination information. **OBJECTIVE:** We reanalyzed the data to explore the hypothesis that VAS reduces mortality in children who had bacille Calmette-Guérin or

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measles vaccine as their most recent vaccine but increased mortality when diphtheria-tetanus-pertussis vaccine (DTP) was the most recent vaccine. On the basis of previous studies, we expected the effects to be strongest in girls. **DESIGN: At enrollment, children aged 6-90 mo were randomly assigned to receive VAS or placebo every 4 mo for 2 y.** Vaccination status was assessed at enrollment and after 1 and 2 y by reviewing the children's health cards. Lack of a health card was presumed to mean that the child had not been vaccinated. **RESULTS: VAS had a beneficial effect only in children with no record of vaccination at enrollment (n = 5066); the mortality rate ratio (MRR) was 0.64 (95% CI: 0.47, 0.88) compared with 0.95 (95% CI: 0.72, 1.26) in children with one or more vaccinations (n = 6656).** Among vaccinated children, the effect of VAS differed between boys (MRR: 0.74; 95% CI: 0.51, 1.08) and girls (MRR: 1.18; 95% CI: 0.84, 1.67) (P = 0.046 for interaction). **VAS had a negative effect in measles-vaccinated girls who were missing one or more doses of DTP at enrollment, a group who often received DTP during follow-up (MRR: 2.60; 95% CI: 1.41, 4.80).** **CONCLUSIONS: The effect of VAS differed by vaccination status. This is potentially problematic because VAS is provided at vaccination contacts.**

Comment

Similar effects were shown by the same authors with a second dose of BCG vaccine, which was associated with higher mortality in infants who had not yet received their booster dose of DTP prior to BCG revaccination. The interaction between vaccines and other immunostimulants, such as vitamin A, vaccine heterologous (non-specific) effects, which may be different in girls than boys need further study in other locations. These interactions have importance for the order of the immunization schedule in high mortality regions.

Vitamin D and calcium

Arch Dis Child. 2009 Dec;94(12):932-7. Epub 2009 Aug 9.

Oral calcium supplementation reverses the biochemical pattern of parathyroid hormone resistance in underprivileged Indian toddlers.

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Abstract

BACKGROUND: Toddlers in Pune, India, accustomed to low dietary calcium intake but vitamin D replete have low serum ionised calcium and inappropriately raised serum inorganic phosphorus concentrations together with elevated serum parathyroid hormone (PTH) concentrations. We hypothesised that dietary calcium deficiency leads to end organ resistance to PTH, thus resulting in mild hypocalcaemia and hyperphosphataemia, and that this would be reversed by oral calcium supplementation. **METHODS:** 51 subjects (25 male; mean (SD) age 2.4 (0.8) years) from an urban slum in Pune were randomised to 500 mg of oral calcium

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supplement or placebo, daily, for 8 weeks. All subjects received 20 mg of oral elemental iron, daily, as 90% had a serum ferritin concentration <12 microg/l. All subjects were examined for clinical stigmata of rickets and had a wrist radiograph performed. Serum concentrations of ionised calcium, phosphorus, PTH and fibroblast growth factor-23 (FGF-23) were measured at the start and end of the trial. RESULTS: No subject had clinical or radiological evidence of rickets. There was a significant increase in mean serum ionised calcium concentration ($p < 0.001$) in the supplemented but not the placebo group ($p = 0.32$). The decrease in mean serum phosphorus concentration in the supplemented group was greater ($p < 0.001$) than in the placebo group ($p = 0.003$). Mean serum PTH fell in the calcium supplemented ($p = 0.001$) but not in the placebo ($p = 0.303$) group. The mean serum FGF-23 concentration did not change in response to calcium supplementation. CONCLUSIONS: From these data the authors conclude that low dietary calcium intake is associated with resistance to PTH.

Br J Nutr. 2010 Mar;103(5):714-23. Epub 2009 Oct 9.

The association between dietary protein intake and bone mass accretion in pubertal girls with low calcium intakes.

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Abstract

To assess the association between protein intakes and bone mass accrual in girls, data were analysed for 757 pre-pubertal girls (mean age 10.1 years) in urban Beijing, China, who participated in a 5-year study including 2 years of milk supplementation (intervention groups only) and 3 years of follow-up study. At 0, 12, 24, 48 and 60 months from the baseline, bone mass of the proximal or distal forearm (PF or DF) and total body (TB) was measured with dual energy X-ray absorptiometry; dietary intakes were assessed by a 3-d food record (including two weekdays and one weekend day). Linear mixed models were used and continuous variables were logarithm transformed. The mean longitudinal Ca intake (432-675 mg/d on average) positively influenced bone mineral content (BMC) at TB, PF and DF after controlling for baseline bone mass and other possible confounders. However, negative associations were observed between protein intake (55.9-61.0 g/d on average) and BMC accrual at TB, PF or DF ($\beta = -1.92, -10.2$ or -4.82 , respectively, $P < 0.01$) after adjustment. When protein intake was considered according to animal or plant food sources, protein from animal foods, particularly meat, had significant negative effects on BMC accrual at DF or PF after adjustment. It was concluded that higher protein intake, especially from animal foods, appeared to have a negative effect on bone mass accrual in Chinese pubertal girls with low Ca intakes.

J Clin Endocrinol Metab. 2009 Sep;94(9):3314-21. Epub 2009 Jun 30.

The effect of vitamin D2 and vitamin D3 on intestinal calcium absorption in Nigerian children with rickets.

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Abstract

CONTEXT: Children with calcium-deficiency rickets have high 1,25-dihydroxyvitamin D values. **OBJECTIVE:** The objective of the study was to determine whether vitamin D increased calcium absorption. **DESIGN:** This was an experimental study. **SETTING:** The study was conducted at a teaching hospital. **PARTICIPANTS:** Participants included 17 children with nutritional rickets. **INTERVENTION:** The participants were randomized to 1.25 mg oral vitamin D(3) (n = 8) or vitamin D(2) (n = 9). **MAIN OUTCOME MEASURE:** Fractional calcium absorption 3 da after vitamin D administration was measured. **RESULTS:** Mean baseline 25-hydroxyvitamin D concentrations were 20 ng/ml (range 5-31 ng/ml). The increase in 25-hydroxyvitamin D was equivalent after vitamin D(3) (29 +/- 10 ng/ml) or vitamin D(2) (29 +/- 17 ng/ml). Mean 1,25-dihydroxyvitamin D values increased from 143 +/- 76 pg/ml to 243 +/- 102 pg/ml (P = 0.001), and the increase in 1,25-dihydroxyvitamin D did not differ between vitamin D(2) and vitamin D(3) (107 +/- 110 and 91 +/- 102 ng/ml, respectively). The increment in 1,25-dihydroxyvitamin D was explained almost entirely by the baseline 25-hydroxyvitamin D concentration ($r(2) = 0.72$; $P < 0.001$). Mean fractional calcium absorption did not differ before (52.6 +/- 21.4%) or after (53.2 +/- 23.5%) vitamin D, and effects of vitamin D(2) and vitamin D(3) on calcium absorption were not significantly different. Fractional calcium absorption was not closely related to concentrations of 25-hydroxyvitamin D ($r = 0.01$, $P = 0.93$) or 1,25-dihydroxyvitamin D ($r = 0.21$, $P = 0.24$). The effect of vitamin D on calcium absorption did not vary with baseline 25-hydroxyvitamin D values or with the absolute increase in 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D values. **CONCLUSIONS:** Despite similar increases in 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D with vitamin D(2) or vitamin D(3), fractional calcium absorption did not increase, indicating that rickets in Nigerian children is not primarily due to vitamin D-deficient calcium malabsorption.

Zinc

(see also: Acute respiratory infection, Diarrhoea, Vitamin A, Cholera vaccine)

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Influence of zinc supplementation in acute diarrhea differs by the isolated organism.

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Abstract

Zinc supplementation is recommended in all acute diarrheas in children from developing countries. We aimed to assess whether zinc supplementation would be equally effective against all the common organisms associated with acute diarrheas. We used data on 801 children with

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acute diarrhea recruited in a randomized, double blind controlled trial (ISRCTN85071383) of zinc and copper supplementation. Using prespecified subgroup analyses, multidimensionality reduction analyses, tests of heterogeneity, and stepwise logistic regression for tests of interactions, we found that the **influence of zinc on the risk of diarrhea for more than 3 days depended on the isolated organism-beneficial in Klebsiella, neutral in Esherichia coli and parasitic infections, and detrimental in rotavirus coinfections.** Although we found similar results for the outcome of high stool volume, the results did not reach statistical significance. Our findings suggest that the current strategy of zinc supplementation in all cases of acute diarrheas in children may need appropriate fine tuning to optimize the therapeutic benefit based on the causative organism, but further studies need to confirm and extend our findings.

Comment

It seems highly unlikely that zinc supplementation would be detrimental in rotavirus infections, as was found in this study, given the overwhelming evidence for zinc in acute watery diarrhoea, and the fact that rotavirus causes 30-50% of the cases of childhood diarrhoea in virtually all countries studied.

Am J Clin Nutr. 2010 Jul;92(1):130-6. Epub 2010 May 19.

Maternal gestational zinc supplementation does not influence multiple aspects of child development at 54 mo of age in Peru.

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Abstract

BACKGROUND: Zinc is necessary for central nervous system development, and maternal zinc status has been associated with developmental differences in offspring. **OBJECTIVE:** The objective was to evaluate differences in cognitive, social, and behavioral function in Peruvian children at 54 mo of age whose mothers participated during pregnancy in a zinc supplementation trial. **DESIGN:** We attempted to follow up 205 children from a prenatal zinc supplementation trial and present data on 184 (90%) children-86 whose mothers took 25 mg zinc/d in addition to 60 mg iron and 250 microg folic acid and 98 whose mothers took iron and folic acid only. Following a standardized protocol, we assessed children's intelligence, language and number skills, representational ability, interpersonal understanding, and adaptive behavior and behavioral adjustment. We also assessed aspects of the mother (eg, age, education, verbal intelligence, stresses, and social support in parenting) and the home environment [HOME (Home Observation for the Measurement of the Environment) inventory]. **RESULTS: No differences were observed between any of the tests used to characterize cognitive, social, or behavioral development (P > 0.05).** Child sex, parity, or treatment compliance did not modify the effects of supplementation on any outcomes. **CONCLUSION: The addition of zinc to prenatal supplements did not influence developmental outcomes in Peruvian children when assessed at 4.5 y of age.**

J Nutr. 2010 Mar;140(3):630-4. Epub 2010 Jan 27.

Zinc supplementation for four months does not affect growth in young north Indian children.

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Abstract

Our objective in this trial was to assess the impact of daily zinc supplementation on growth in young children. A double-blind, randomized, placebo-controlled trial was conducted in New Delhi, India. We enrolled 2482 children aged 6-30 mo who were supplemented daily with placebo or zinc (10 mg elemental zinc to infants and 20 mg to older children) for 4 mo. **At enrollment, all children also received a single dose of vitamin A (104.7 micromol for infants and 209.4 micromol for older children). Weight and length were measured at enrollment and 4 mo later.** Weekly visits were conducted by field workers to ascertain morbidity in the previous 7 d. Change in length, weight, length-for-age Z-scores (LAZ), and weight-for-length Z-scores (WLZ) after 4 mo of supplementation were assessed in the zinc and placebo groups. **After 4 mo of supplementation, the weight and length gains in the 2 groups did not differ and there was no impact on LAZ, weight-for-age, and WLZ in the 2 groups.** There was no substantial effect in any of the subgroups defined for age, income, gender, zinc levels in the crude analysis nor after adjusting for age, gender, income, breast-feeding status, and baseline anthropometric status. **Despite successful zinc supplementation reflected in increased plasma zinc concentration and a substantially reduced incidence of diarrhea and pneumonia in zinc-supplemented children, the intervention did not have a beneficial effect on growth.**

J Health Popul Nutr. 2009 Oct;27(5):632-9.

Zinc deficiency: descriptive epidemiology and morbidity among preschool children in peri-urban population in Delhi, India.

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Abstract

Community-based data relating to factors influencing zinc deficiency among preschool children in India are inadequate. Data of a large, double-blinded, randomized, controlled zinc-supplementation trial were used for assessing the descriptive epidemiology of zinc deficiency

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among children aged 6-35 months (n = 940). In total, 609 children were followed up for 120 days for information on morbidity. Of these children, 116 from the control group belonging to the upper and the lower 25th quartile of plasma zinc status at baseline were selected for assessing the association of zinc deficiency with prospective morbidity. At baseline, demographic, socioeconomic and dietary information was collected, and anthropometric measurements and levels of plasma zinc were assessed. At baseline, 73.3% of the children were zinc-deficient (plasma zinc < 70 microg/dL), of which 33.8% had levels of plasma zinc below 60 microg/dL. **A significantly higher risk of morbidity was prevalent among the subjects with lower plasma zinc compared to those with higher levels of plasma zinc.**