

RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

5th Edition
July 2006-June 2007

www.ichrc.org

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SEARCH STRATEGY

Pubmed Hayne's strategy, search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR Asia-Pacific) and (Child*)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])).

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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.

Several trials from 2006-07 will lead to significant changes in child health recommendations. Some of the key findings include:

- Isoniazid prophylaxis in HIV-infected children living in areas endemic for tuberculosis substantially lowers mortality
- Formula feeding was associated with higher risk of mortality in infants of HIV-affected mothers in Botswana (despite a lower risk of HIV transmission)
- In HIV-infected children cotrimoxazole prophylaxis reduces mortality (confirmed data from a 2004 trial)
- In children with measles, antibiotic prophylaxis (using cotrimoxazole) reduces the risk of pneumonia and other serious complications
- Routine iron *supplementation* increases the risk of diarrhoea and malaria morbidity in malaria endemic areas (confirmed results of a 2005 trial)...conversely
- Iron and zinc *fortification* of milk reduced diarrhoeal disease and ARI morbidity in 1-3 year olds in north India
- Fractional doses of Hib vaccine provide an effective immune response (confirming studies from 2002)

This year we have included the web-link for 26 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 3750 journals are available to health institutions in 113 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 copy this booklet and distribute it to colleagues. Previous editions (2002-2006) are available at: www.ichrc.org

Trevor Duke
August 2007

Acute respiratory infection

(See also Measles)

Int J Tuberc Lung Dis. 2006 Aug;10(8):924-31.

Can WHO therapy failure criteria for non-severe pneumonia be improved in children aged 2-59 months?

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SETTING: In the recent past, there have been reports of rising treatment failure rates for non-severe pneumonia. It is felt that World Health Organization (WHO) criteria for therapy failure are too sensitive and that many children are unnecessarily classified as failures. We studied alternative, less sensitive therapy failure criteria. **METHODS:** In this nested study we followed the clinical course of non-severe pneumonia in children aged 2-59 months using alternative therapy failure criteria. All children received amoxicillin and were followed up on days 3, 5 and 14 after enrollment. On day 3, children were labelled as therapy failure only if their condition had deteriorated. These failure rates were compared with those using WHO definitions. **RESULTS:** During the study period, 876 children with non-severe pneumonia were followed up until day 14. On day 3, using alternative therapy failure criteria, 31 (3.5%) children were labelled as therapy failure compared to 95 (10.8%) using current WHO criteria. The difference was statistically significant ($P = 0.001$). **CONCLUSIONS:** The alternative therapy failure criteria work reasonably well, without causing any higher risk to children with non-severe pneumonia. Antibiotics should be changed only in those children who show signs of deterioration on day 3. This would prevent unnecessary changes in antibiotic treatment in many children.

Asthma

J Pak Med Assoc. 2006 Dec;56(12):595-9.

Management of acute asthma in children using metered dose inhaler and small volume nebulizer.

Jamalvi SW, Raza SJ, Naz F, Shamim S, Jamalvi SM.

Department of Pediatrics, Jinnah Medical and Dental College, Karachi.

OBJECTIVE: To determine whether the administration of beta2-agonist by Metered Dose inhaler (MDI) with accessory device (AD) is as effective as the administration of beta2-agonist by small volume nebulizers (SVN) for the treatment of acute asthma. **METHODS:** A cross sectional study was conducted at Emergency Room (ER) of National Institute of Child

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Health (NICH), Karachi, between October 2000 to March 2001. This study included 150 children, 6 months and older with a history of wheeze and presenting with an acute asthma exacerbation. Children were categorized into mild, moderate and severe asthma according to medical scoring system. Children were assigned randomly into group A and B to receive standard dose of beta2-agonist (salbutamol) by MDI/AD (group A) or SVN (group B). Baseline characteristics and asthma severity were recorded. All variables (dyspnoea, use of accessory muscles, cyanosis, respiratory rate, heart rate, blood pressure, oxygen saturation, pulsus paradoxus, and wheeze) and Peak Expiratory Flow Rate (PEFR) in children 5 years and older, were determined at pre and post inhalation therapy. **RESULTS:** Both groups did not differ in demographic characteristics. There were no significant differences in outcome measures. In children treated with MDI/ADs and SVNs. PEFR increased significantly in both the groups after completion of treatment, but PEFR was not statistically significant when compared in between groups. **CONCLUSION:** The data suggested that MDI/AD is an effective alternative to nebulizer for the treatment of children with acute asthma exacerbation in the ER.

Chronic Illn. 2005 Mar;1(1):31-8.

A trial of asthma self-management in Beijing schools.

Clark NM, Gong M, Kaciroti N, Yu J, Wu G, Zeng Z, Wu Z.

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OBJECTIVES: This study examined the effectiveness in children in China of an asthma education programme adapted from a model developed in the USA. **METHODS:** Six hundred and thirty-nine children in 21 elementary schools in one agricultural and one industrial area participated in a randomized, controlled trial. Data were collected at baseline and 1 year subsequently. The self-regulation-based programme addressed topics including preventing and managing symptoms, using medicines, and identifying and controlling triggers. **RESULTS:** Positive effects on treatment children v. control children were noted in school performance (0.21 v. -0.06, $p=0.04$), absences (-0.55 v. -0.32, $p=0.02$), and home environment (1.78 v. 4.75, $p=0.009$). Industrial-area children additionally benefited from fewer hospitalizations (odds ratio =1.96, $p=0.05$) and asthma-related concerns of parents (-0.63 v. -0.34, $p=0.001$). Agricultural-area parents showed greater improvement in asthma management (0.93 v. 0.26, $p=0.0001$), and expressed more negative feelings about asthma (-0.13 v. -0.58, $p=0.04$) and asthma concerns (-0.31 v. -0.63, $p=0.0001$). **DISCUSSION:** The programme provided overall benefits related to school performance, absences, and home environment. In the agricultural area, where fewer resources were available, benefits were fewer and concerns greater. In the industrial area, where education and income were higher, additional benefits related to healthcare use and parents' quality of life were realized.

Development

Arch Phys Med Rehabil. 2007 Jan;88(1):25-31.

Effectiveness of loaded sit-to-stand resistance exercise for children with mild spastic diplegia: a randomized clinical trial.

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OBJECTIVE: To investigate effectiveness of a functional strengthening program, the loaded sit-to-stand (STS) resistance exercise, for children with cerebral palsy (CP). **DESIGN:** A single-blind, randomized block design. **SETTING:** STS exercises were carried out at the children's homes. **PARTICIPANTS:** Twenty children (12 boys, 8 girls; age range, 5-12y) with spastic diplegia CP and classified by the Gross Motor Function Classification System as level I or II were stratified by their severity and age and randomly allocated into either the experimental or control group. **INTERVENTION:** Both groups received their regular physical therapy. The experimental group underwent loaded STS exercise 3 times a week for 6 weeks. **MAIN OUTCOME MEASURES:** Goal dimension scores of the Gross Motor Function Measure (GMFM), gait speed, 1 repetition maximum (1-RM) of the loaded STS, isometric strength of knee extensor, and Physiological Cost Index (PCI). The outcome measures were conducted at the beginning and end of the 6-week study. **RESULTS:** After loaded STS exercise, the experimental group showed statistically significant differences in GMFM goal dimension scores, 1-RM STS, and PCI from the control group. The changes in gait speed and isometric strength of the knee extensor did not differ significantly between the 2 groups. **CONCLUSIONS:** After the loaded STS exercise, children with mild spastic diplegia improved their basic motor abilities, functional muscle strength, and walking efficiency.

J Nutr. 2006 Sep;136(9):2427-34.

Combined iron and folic acid supplementation with or without zinc reduces time to walking unassisted among Zanzibari infants 5- to 11-mo old.

Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Stoltzfus RJ.

U.S. Department of Agriculture, ARS-Western Human Nutrition Research Center, Davis, CA, USA.

Iron and zinc deficiencies have been associated with delayed motor development in nutritionally at-risk children, albeit inconsistently. In this community-based, randomized double-blind trial, iron+folic acid (FeFA) (12.5 mg Fe + 50 mug folic acid), zinc (Zn) (10 mg), and iron+folic acid+zinc (FeFA+Zn) supplements or a placebo were given daily for 1 y to nutritionally at-risk children in Pemba, Zanzibar. The effects of these treatments on attaining unassisted walking were evaluated using survival analysis for 354 children aged 5-11 mo at the start of supplementation. Treatment effects on changes in hemoglobin (Hb) and zinc protoporphyrin (ZPP) and height-for-age (HAZ) and weight-for-age (WAZ) Z scores were evaluated using linear regression. Attained motor milestone was recorded every 2 wk for 1 y. Hb, ZPP, HAZ, and WAZ were measured at baseline and after 6 mo of treatment. FeFA with or without Zn

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reduced the time it took for children to walk assisted. Children who received any iron walked unassisted sooner than those who received no iron [median difference approximately 15 d, $P = 0.035$, risk ratio (RR) = 1.28, 95% CI = 1.02, 1.61] and this effect was stronger in those who had iron deficiency anemia (IDA) at baseline (median difference was approximately 30 d; $P = 0.002$; RR = 1.68; 95% CI = 1.21, 2.32). FeFA alone and Zn alone improved Hb and ZPP compared with placebo. There were no significant treatment effects on changes in HAZ or WAZ. The effects of treatment on time to walking may have been mediated by improvements in iron status or hemoglobin, but were not mediated through improvements in growth.

J Child Adolesc Psychopharmacol. 2006 Aug;16(4):441-55.

An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan.

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This study examined the efficacy and safety of osmotic release oral system methylphenidate (OROS MPH) as compared with immediate-release MPH (IR MPH) in children with attention-deficit/hyperactivity disorder (ADHD) in Taiwan. Sixty-four children with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) ADHD, ages 6-15 years, were randomized to OROS MPH once daily ($n = 32$) and IR MPH three times daily ($n = 32$) in an open, randomized, active-controlled equivalent 28-day trial. The main outcome measures included the Conner's Teacher Rating Scale -Revised: Short Form and Conner's Parent Rating Scale-Revised: Short Form, and other measures of social adjustment and side effects. Results showed significant reductions in the core ADHD symptoms, which did not differ between the two treatment groups. Compared to the IR MPH group, the OROS MPH group showed a significantly greater slope of reductions in ADHD symptoms and decline in the severity of problems at school, and with peers and parents over time. There was no difference in rates of side effect profile between the two groups. Our findings suggest that OROS MPH is superior over IR MPH in the greater magnitude of improvement over study period without increased side effects in the Chinese population.

Diarrhoeal disease

(See also Public Health / Hygiene and Zinc)

J Health Popul Nutr. 2007 Mar;25(1):67-74.

Impact of zinc supplementation on subsequent morbidity and growth in Bangladeshi children with persistent diarrhoea.

Roy SK, Tomkins AM, Akramuzzaman SM, Chakraborty B, Ara G, Biswas R, Islam KE,

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This study was conducted to explore whether supplementation of zinc to children during persistent diarrhoea has any subsequent effect on morbidity and growth. A prospective follow-up study was conducted among children, aged 3-24 months, with persistent diarrhoea, who participated earlier in a double-blind randomized placebo-controlled trial. During persistent diarrhoea, children were randomly allocated to receive either zinc in multivitamin syrup or only multivitamin syrup for two weeks. After recovering from diarrhoea, 76 children in the multivitamin syrup and 78 children in the zinc plus multivitamin syrup group were followed up for subsequent morbidity and growth. Weekly morbidity and two-weekly anthropometric data were collected for the subsequent 12 weeks. Data showed that episodes and duration of diarrhoea were reduced by 38% and 44% respectively with supplementation of zinc. There was no significant difference in the incidence or duration of respiratory tract infection between the zinc-supplemented and the non-supplemented group. Improved linear growth was observed in underweight children (weight-for-age <70% of the National Center for Health Statistics standard) who received zinc compared to those who did not receive.

J Pediatr Gastroenterol Nutr. 2007 Feb;44(2):258-64.

Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea.

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OBJECTIVE: To compare glucose and rice-based oral rehydration solution with rice-based oral rehydration solution containing recombinant human lactoferrin and recombinant human lysozyme in diarrhea outcomes. **PATIENTS AND METHODS:** We conducted a randomized, double-blind controlled trial in children with acute diarrhea and dehydration. One hundred and forty children 5 to 33 months old were block randomized to receive low osmolarity WHO-ORS (G-ORS), rice-based ORS (R-ORS), or rice-based ORS plus lactoferrin and lysozyme (Lf/Lz-R-ORS). Intake and output were monitored for 48 h in the ORU, with continued monitoring through home and clinic follow-up for 14 d. **RESULTS:** The G-ORS and R-ORS groups did not show any differences in diarrhea outcomes and were therefore combined as the control group. Intent-to-treat analysis showed a significant decrease in duration of diarrhea (3.67 d vs 5.21 d, $P = 0.05$) in the Lf/Lz-R-ORS group as compared with the control group and a significant increase in the number of children who achieved 48 h with solid stool, 85% vs 69% ($P < 0.05$). There were also decreases in volume of diarrhea and the percentage of children who had a new diarrhea episode after achieving the endpoint. **CONCLUSIONS:** Addition of recombinant human lactoferrin and lysozyme to a rice-based oral rehydration solution had beneficial effects on children with acute diarrhea.

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Int J Food Microbiol. 2006 Aug 1;110(3):246-53. Epub 2006 Jun 30.

Spontaneously fermented millet product as a natural probiotic treatment for diarrhoea in young children: an intervention study in Northern Ghana.

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Indigenous lactic acid fermented foods may have potential as probiotic treatment for diarrhoea, due to high levels of lactic acid bacteria. In this study the effect of a millet drink, spontaneously fermented by lactic acid bacteria, as a therapeutic agent among Ghanaian children with diarrhoea, was assessed. Children below 5 years of age coming to Northern Ghana health clinics for treatment of diarrhoea were randomised to two groups. Children of both groups received treatment for diarrhoea given at the local clinic. The intervention group in addition received up to 300 ml fermented millet drink (KSW) daily for 5 days after enrolment. The clinical outcome of diarrhoea and reported well-being were registered every day for the 5-day intervention and again 14 days after diagnosis. Among 184 children (mean age 17.4, standard deviation 11.3 months) included, no effects of the intervention were found with respect to stool frequency, stool consistency and duration of diarrhoea. However, KSW was associated with greater reported well-being 14 days after the start of the intervention ($P=0.02$). The fact that no effect of KSW on diarrhoea was observed could be because many children had a mild form of diarrhoea, and many were treated with antibiotics. Either this could have affected the lactic acid bacteria, or the lactic acid bacteria in KSW had no probiotic effects. It is speculated that the effect after two weeks could be due to a preventing effect of KSW on antibiotic-associated diarrhoea which could help reducing persistent diarrhoea.

Ear disease

East Afr Med J. 2006 Jun;83(6):322-5.

Chronic suppurative otitis media in Tanzanian school children and its effects on hearing.

Minja BM, Moshi NH, Ingvarsson L, Bastos I, Grenner J.

ORL Department, Muhimbili University College of Health Sciences, P.O. Box 650001, Dar es Salaam, Tanzania.

OBJECTIVES: To compare different treatment regimens of chronic suppurative otitis media (CSOM) in school children, in regard to their consequence in hearing and discharge from the ear drum perforation. **DESIGN:** Randomised controlled trial. **SETTING:** Randomly selected primary schools within Dar es Salaam. **SUBJECTS:** Three hundred and twenty eight children

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between 5-17 years of age with CSOM in one or both ears. RESULTS: Three to four months after the onset of treatment 31% of group 1, 54% of group 2, and 56% of group 3, had dry ears. Treatment with dry mopping and boric acid in alcohol ear drops was significantly better than dry mopping alone. Adding amoxicillin to the treatment did not improve the end results. Hearing test performed before and after treatment showed that the hearing thresholds were the same or better after the treatment. The possible risk that boric acid in alcohol ear drops should lead to sensorineural hearing loss has not been confirmed. CONCLUSION: Based on the above results, the treatment of choice for CSOM in children in Dar es Salaam should be dry mopping and boric acid in spirit ear drops.

Epilepsy

Neurology. 2006 Jul 25;67(2):340-2.

Sodium valproate vs phenytoin in status epilepticus: a pilot study.

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Sixty-eight patients with convulsive status epilepticus (SE) were randomly assigned to two groups to study the efficacy of sodium valproate (VPA) and phenytoin (PHT). Seizures were aborted in 66% in the VPA group and 42% in the PHT group. As a second choice in refractory patients, VPA was effective in 79% and PHT was effective in 25%. The side effects in the two groups did not differ. Sodium valproate may be preferred in convulsive SE because of its higher efficacy.

Filariasis

Ann Trop Med Parasitol. 2007 Jul;101(5):423-33.

Children and adolescents infected with Wuchereria bancrofti in Greater Recife, Brazil: a randomized, year-long clinical trial of single treatments with diethylcarbamazine or diethylcarbamazine-albendazole.

Rizzo JA, Belo C, Lins R, Dreyer G.

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In filariasis-endemic areas beyond sub-Saharan Africa, the World Health Organization's recommended strategy for interrupting transmission of the causative parasites is annual, single-dose, mass treatment with a combination of diethylcarbamazine (DEC; given at 6 mg/kg) and albendazole (ALB; given at 400 mg) for 4-6 years (the minimum estimated life-span of the adult parasites). In an open, hospital-based, randomized and controlled trial, with a blinded evaluation of outcome, 82 children and adolescents from Recife, all with *Wuchereria bancrofti* microfilaraemias, were given either DEC alone (6 mg/kg) or the same dose of DEC combined with ALB (at 400 mg/patient). Every 90 days for 1 year after the single treatment, each patient was checked for microfilaraemia by the filtration of up to 5 ml of venous blood collected at night. One year post-treatment, 16 (39%) of the 41 patients given DEC alone and 20 (49%) of the 41 given DEC-ALB were found microfilaraemic (relative risk=0.8, with a 95% confidence interval of 0.49-1.31) and the corresponding geometric mean levels of microfilaraemia were 2.0% and 1.8% of the levels recorded immediately pre-treatment, respectively ($P>0.05$). In terms of the prevalences and intensities of microfilaraemia, therefore, the addition of ALB to the DEC appeared to offer no significant benefit.

Gastrointestinal parasitic infections

Southeast Asian J Trop Med Public Health. 2006;37 Suppl 3:32-4.

Randomized comparative trial of two high-dose albendazole regimens for uncomplicated human strongyloidiasis.

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Office of Disease Prevention and Control 6 Khon Kaen, Department of Disease Control, Ministry of Public Health, Khon Kaen, Thailand.

A randomized trial study was conducted comparing the efficacy of two high-dose regimens of albendazole for the treatment of uncomplicated human strongyloidiasis. Agar plate culture (APC) was used as an evaluation technique for coprological diagnosis. All 115 subjects infected with *Strongyloides stercoralis* from 7 provinces in northeastern Thailand were divided randomly into two groups. Regimen-1 group received albendazole 800 mg/day twice daily for 3 consecutive days, and regimen-2 group received the same dose for 5 consecutive days. For each regimen, the same treatment was repeated once 7 days later. Stools were parasitologically examined at 14 days, and 10 days after the second course of treatment, respectively. A coprological cure rate of 87.9% (51/58) was obtained in the regimen-1 group, with 89.5% (51/57) in the regimen-2 group, which was not statistically significantly different ($P = 0.794$). The mild adverse effects were not statistically different between the two groups, at 8.6% and 8.8%, respectively ($P = 0.977$). We therefore suggest albendazole treatment using regimen 1 should be recommended. However, the use of new effective drugs should be considered, especially in hyperinfective strongyloidiasis.

Am J Trop Med Hyg. 2007 Apr;76(4):732-6.

Low efficacy of mebendazole against hookworm in Vietnam: two randomized

controlled trials.

Flohr C, Tuyen LN, Lewis S, Minh TT, Campbell J, Britton J, Williams H, Hien TT, Farrar J, Quinell RJ.

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Vietnam is participating in a global de-worming effort that aims to treat 650 million school children regularly by 2010. The treatment used in Vietnam is single dose oral mebendazole (Phardazone) 500 mg. We tested the efficacy of single dose mebendazole 500 mg in the therapy of hookworm infection in a randomized double-blind placebo-controlled trial among 271 Vietnamese schoolchildren. The treatment efficacy of single dose mebendazole in children did not differ significantly from placebo, with a reduction in mean eggs per gram of feces relative to placebo of 31% (95% CI -9 to 56%, $P = 0.1$). In light of these findings we then carried out a similar randomized trial comparing triple dose mebendazole, single dose albendazole, and triple dose albendazole against placebo in 209 adults in the same area. The estimated reduction in mean post-treatment eggs per gram of feces relative to placebo was 63% (95% CI 30-81%) for triple mebendazole, 75% (47-88%) for single albendazole, and 88% (58-97%) for triple albendazole. Our results suggest that single dose oral mebendazole has low efficacy against hookworm infection in Vietnam, and that it should be replaced by albendazole. These findings are of major public health relevance given the opportunity costs of treating entire populations with ineffective therapies. We recommend that efficacy of anti-helminth therapies is pilot tested before implementation of national gut worm control programs.

East Mediterr Health J. 2006 Sep;12(5):548-54.

Albendazole versus metronidazole in the treatment of patients with giardiasis in the Islamic Republic of Iran.

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We examined the therapeutic effects of albendazole compared to metronidazole in 120 patients with giardiasis in Hamdan. Patients were randomized to receive albendazole (400 mg, once daily for 5 days) or metronidazole (250 mg, 3 times a day for 5 days). Demographic data of the patients, results of stool examination for *Giardia* trophozoites before and after treatment, and drug side-effects were recorded. After treatment 6 (10.0%) of the albendazole group had trophozoites compared with 14 (23.3%) of metronidazole group ($P < 0.05$). Patients in the albendazole group had fewer side-effects while 43.3% of the metronidazole group experienced a metallic taste and 35.0% experienced loss of appetite. Albendazole is an easy, safe and effective treatment for giardiasis.

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Clin Trials. 2007;4(1):42-57.

The impact of helminths on the response to immunization and on the incidence of infection and disease in childhood in Uganda: design of a randomized, double-blind, placebo-controlled, factorial trial of deworming interventions delivered in pregnancy and early childhood [ISRCTN32849447].

Elliott AM, Kizza M, Quigley MA, Ndibazza J, Nampijja M, Muhangi L, Morison L, Namujju PB, Muwanga M, Kabatereine N, Whitworth JA.

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BACKGROUND: Helminths have profound effects on the immune response, allowing long-term survival of parasites with minimal damage to the host. Some of these effects "spill-over", altering responses to non-helminth antigens or allergens. It is suggested that this may lead to impaired responses to immunizations and infections, while conferring benefits against inflammatory responses in allergic and autoimmune disease. These effects might develop in utero, through exposure to maternal helminth infections, or through direct exposure in later life. **PURPOSE:** To determine the effects of helminths and their treatment in pregnancy and in young children on immunological and disease outcomes in childhood. **METHODS:** The trial has three randomized, double-blind, placebo-controlled interventions at two times, in two people: a pregnant woman and her child. Pregnant women are randomized to albendazole or placebo and praziquantel or placebo. At age 15 months their children are randomized to three-monthly albendazole or placebo, to continue to age five years. The proposed designation for this sequence of interventions is a 2 x 2(x2) factorial design. Children are immunized with BCG and against polio, Diphtheria, tetanus, Pertussis, Haemophilus, hepatitis B and measles. Primary immunological outcomes are responses to BCG antigens and tetanus toxoid in whole blood cytokine assays and antibody assays at one, three and five years of age. Primary disease outcomes are incidence of malaria, pneumonia, diarrhoea, tuberculosis, measles, vertical HIV transmission, and atopic disease episodes, measured at clinic visits and twice-monthly home visits. Effects on anaemia, growth and intellectual development are also assessed. **CONCLUSION:** This trial, with a novel design comprising related interventions in pregnant women and their offspring, is the first to examine effects of helminths and their treatment in pregnancy and early childhood on immunological, infectious disease and allergic disease outcomes. The results will enhance understanding of both detrimental and beneficial effects of helminth infection and inform policy.

BMJ. 2006 Jul 15;333(7559):122. Epub 2006 Jun 21.

<http://www.bmj.com/cgi/content/full/333/7559/122>

Effect on weight gain of routinely giving albendazole to preschool children during child health days in Uganda: cluster randomised controlled trial.

Alderman H, Konde-Lule J, Sebuliba I, Bundy D, Hall A.

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OBJECTIVE: To estimate the effectiveness of delivering an anthelmintic through a community

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child health programme on the weight gain of preschool children in Uganda. DESIGN: Cluster randomised controlled trial. SETTING: Eastern Uganda. PARTICIPANTS: 48 parishes participating in a new programme for child health: 24 offered children an additional service of anthelmintic treatment. The outcome is based on measurements from 27,995 children. INTERVENTION: Treatment of children aged between 1 and 7 years with 400 mg albendazole added to standard services offered during child health days over a three year period. MAIN OUTCOME MEASURE: Weight gain. RESULTS: The provision of periodic anthelmintic treatment as a part of child health services in Uganda resulted in an increase in weight gain of about 10% (166 g per child per year, 95% confidence interval 16 to 316) above expected weight gain when treatments were given twice a year, and an increase of 5% when the treatment was given annually. CONCLUSION: Deworming of preschool children in Uganda as part of regularly scheduled health services seems practical and associated with increased weight gain.

Comment

This important trial shows substantial effects on weight gain in school aged children of deworming with albendazole. Other studies this year showed that albendazole is: more effective than metronidazole at treating giardiasis in Iran; more effective than mebendazole at treating hookworm in Vietnam; as effective if given for 3 days as it is if given for 5 days in Strongyloides infection; but did not add anything to the efficacy of diethylcarbamazine in the mass prevention of filariasis.

HIV / AIDS

Case management and anti-retroviral therapy

BMJ. 2007 Jan 20;334(7585):136. Epub 2006 Nov 3.

<http://www.bmj.com/cgi/content/full/333/7559/122>

Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial.

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OBJECTIVES: To investigate the impact of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV. DESIGN: Two centre prospective double blind placebo controlled trial. PARTICIPANTS: Children aged > or =8 weeks with HIV. INTERVENTIONS: Isoniazid or placebo given with co-trimoxazole either daily or three times a week. SETTING: Two tertiary healthcare centres in South Africa. MAIN OUTCOME MEASURES: Mortality, incidence of tuberculosis, and adverse events. RESULTS: Data on 263 children (median age 24.7 months) were available when the data safety monitoring board recommended discontinuing the placebo arm; 132 (50%) were taking isoniazid. Median follow-up was 5.7 (interquartile range 2.0-9.7) months. Mortality was lower in the isoniazid group than in the placebo group (11 (8%) v 21 (16%), hazard ratio 0.46, 95% confidence interval 0.22 to 0.95, P=0.015) by intention

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to treat analysis. The benefit applied across Centers for Disease Control clinical categories and in all ages. The reduction in mortality was similar in children on three times a week or daily isoniazid. The incidence of tuberculosis was lower in the isoniazid group (5 cases, 3.8%) than in the placebo group (13 cases, 9.9%) (hazard ratio 0.28, 0.10 to 0.78, $P=0.005$). All cases of tuberculosis confirmed by culture were in children in the placebo group. **CONCLUSIONS:** Prophylaxis with isoniazid has an early survival benefit and reduces incidence of tuberculosis in children with HIV. Prophylaxis may offer an effective public health intervention to reduce mortality in such children in settings with a high prevalence of tuberculosis. **TRIAL REGISTRATION:** Clinical Trials NCT00330304.

Comment

This very important study shows the beneficial effect of routine isoniazid in children with HIV living in areas that are endemic for tuberculosis. The effect on mortality was greater than the contribution of TB to mortality. Like cotrimoxazole, shown conclusively in 2004 to reduce mortality in children with HIV, isoniazid should be given to all children with HIV in TB endemic areas.

Clin Infect Dis. 2007 May 15;44(10):1361-7. Epub 2007 Apr 12.

The impact of daily cotrimoxazole prophylaxis and antiretroviral therapy on mortality and hospital admissions in HIV-infected Zambian children.

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BACKGROUND: Data on the population effectiveness of cotrimoxazole prophylaxis and antiretroviral therapy (ART) in human immunodeficiency virus (HIV)-infected African children are few. **METHODS:** A total of 534 Zambian children with HIV infection were randomized to receive daily cotrimoxazole prophylaxis or placebo in the Children with HIV Antibiotic Prophylaxis trial. Following trial closure, children who received the placebo initiated cotrimoxazole prophylaxis, and all children were observed in a closed cohort. Mortality and hospital admission rates were compared, over calendar time, in 9-month periods: trial recruitment (March 2001 to April 2002, May 2002 to January 2003), trial follow-up to closure (February 2003 to October 2003), initial follow-up posttrial (November 2003 to July 2004), and early and later ART availability (August 2004 to April 2005, and May 2005 to May 2006, respectively). **RESULTS:** A total of 546 child-years of follow-up, 40 deaths, and 80 hospital admissions were observed between the time of trial closure and June 2006. A total of 117 of 283 children who were alive at trial closure received ART in the posttrial period (median child age at first use of ART, 8.8 years). Rates decreased in both groups during the trial period, suggesting a survivorship effect. Mortality and hospital admission rates before trial closure were 14 (95% confidence interval [CI], 9-21) deaths per 100 child-years and 24 (95% CI, 15-39) hospital admissions per 100 child-years, respectively, for children who were receiving cotrimoxazole,

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and were 23 (95% CI, 16-34) deaths per 100 child-years and 35 (95% CI, 23-53) hospital admissions per 100 child-years, respectively, for children who were receiving the placebo. After trial closure, rates remained stable in the cotrimoxazole group, but decreased to 15 (95% CI, 8-26) deaths per 100 child-years and 19 (95% CI, 10-41) hospital admissions per 100 child-years, respectively, for the group of children who received placebo and then initiated cotrimoxazole prophylaxis. In both groups combined, mortality rates decreased to 6 (95% CI, 3-11) deaths per 100 child-years and then 2 (95% CI, 0.8-6) deaths per 100 child-years during periods of ART availability; hospital admission rates decreased to 17 (95% CI, 11-27) hospital admissions per 100 child-years and 8 (95% CI, 4-15) hospital admissions per 100 child-years, respectively. CONCLUSION: The benefits of once-daily cotrimoxazole prophylaxis continued throughout the trial and after trial closure. Mortality and hospital admissions decreased (by approximately 6-fold and approximately 3-fold, respectively) following ART availability, similar to findings observed in resource-rich countries.

Comment

The initial results of the above two papers were published in 2004 (Lancet. 2004 Nov 20;364:1865-71). What this paper adds are some effectiveness data. After the trial was completed and children in the control arm were given cotrimoxazole, mortality fell substantially.

AIDS. 2007 Jan 2;21(1):77-84.

Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children.

Mulenga V, Ford D, Walker AS, Mwenya D, Mwansa J, Sinyinza F, Lishimpi K, Nunn A, Gillespie S, Zumla A, Chintu C, Gibb DM; CHAP Trial Team.

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BACKGROUND: Cotrimoxazole prophylaxis reduces morbidity and mortality in HIV-1-infected children, but mechanisms for these benefits are unclear. **METHODS:** CHAP was a randomized trial comparing cotrimoxazole prophylaxis with placebo in HIV-infected children in Zambia where background bacterial resistance to cotrimoxazole is high. We compared causes of mortality and hospital admissions, and antibiotic use between randomized groups. **RESULTS:** Of 534 children (median age, 4.4 years; 32% 1-2 years), 186 died and 166 had one or more hospital admissions not ending in death. Cotrimoxazole prophylaxis was associated with lower mortality, both outside hospital ($P = 0.01$) and following hospital admission ($P = 0.005$). The largest excess of hospital deaths in the placebo group was from respiratory infections [22/56 (39%) placebo versus 10/35 (29%) cotrimoxazole]. By 2 years, the cumulative probability of dying in hospital from a serious bacterial infection (predominantly pneumonia) was 7% on cotrimoxazole and 12% on placebo ($P = 0.08$). There was a trend towards lower admission rates for serious bacterial infections in the cotrimoxazole group (19.1 per 100 child-years at risk versus 28.5 in the placebo group, $P = 0.09$). Despite less total follow-up due to higher mortality, more antibiotics (particularly penicillin) were prescribed in the placebo group in year one [6083 compared to 4972 days in the cotrimoxazole group ($P = 0.05$)]. **CONCLUSIONS:** Cotrimoxazole prophylaxis appears to mainly reduce death and hospital admissions from

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respiratory infections, supported further by lower rates of antibiotic prescribing. As such infections occur at high CD4 cell counts and are common in Africa, the role of continuing cotrimoxazole prophylaxis after starting antiretroviral therapy requires investigation.

Acta Paediatr. 2007 Jan;96(1):62-8.

The effect of nutritional support on weight gain of HIV-infected children with prolonged diarrhoea.

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AIM: To examine the effect on growth and immunity of enhanced calorie and protein provision to HIV-infected children presenting with prolonged diarrhoea. **METHODS:** A total of 169 HIV-infected children aged 6-36 months with diarrhoea for 7 days or more were randomly assigned to either standard nutrition support for children with prolonged diarrhoea or an enhanced diet started during hospitalisation and continued after discharge. The change in weight between enrolment and 8, 14 and 26 weeks and changes in plasma HIV-RNA and CD4 cell count at 8 and 26 weeks were estimated. **RESULTS:** Children receiving enhanced nutrition achieved significantly more weight gain ($p < 0.001$) between enrolment and 8 weeks than children on the standard diet (median increase in weight-for-age standard deviation score +1.02 vs. +0.01). After 8 weeks median weight velocity was normal and similar in both groups. The change in median CD4 count was similar in both groups. The 26-week mortality rate was high in both groups (standard support: 22%, enhanced support: 29%). **CONCLUSIONS:** Nutrition support of children with advanced HIV infection and prolonged diarrhoea resulted in significant and sustained weight gain, but did not improve CD4 counts or survival. These results support integrated nutrition interventions for HIV-infected children.

Antivir Ther. 2006;11(7):857-67.

A randomized controlled trial of genotypic HIV drug resistance testing in HIV-1-infected children: the PERA (PENTA 8) trial.

Green H, Gibb DM, Compagnucci A, Giacomet V, de Rossi A, Harper L, Saïdi Y, Castelli-Gattinara G, Pillay D, Babiker AG, Aboulker JP, Lyall H, Bacheler LT, Walker AS, Debré M, Rosso R, Burger DM, Della Negra M, Dunn DT, Giaquinto C; Paediatric European Network for the Treatment of AIDS.

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OBJECTIVE: To evaluate the longer-term utility of genotypic resistance testing in HIV-1-

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infected children with virological failure. **METHODS:** Children aged 3 months-18 years switching antiretroviral therapy (ART) with HIV-1 RNA > 2,000 copies/ml were randomized between genotypic testing (Virtual Phenotype) and no testing at baseline and subsequent virological failures. Children were followed to at least 96 weeks. **RESULTS:** One hundred and seventy eligible children, from 24 clinical centres in six countries, were randomized to resistance testing (n = 87) or no testing (n = 83) between June 2000-July 2003. At baseline, mean HIV-1 RNA and CD4+ T-cell percentage were 4.7 log₁₀ copies/ml and 20%, respectively. Children had taken ART for a mean of 5 years; 24% had received all three classes, 53% nucleoside reverse transcriptase inhibitors (NRTIs)+protease inhibitors (PIs), 9% NRTIs+non-nucleoside reverse transcriptase inhibitors (NNRTIs) and 14% NRTIs only. There was no difference between the arms in the drug classes or the individual PIs/NNRTIs prescribed. However, 49% in the resistance test arm (RT) versus 19% in the no-test arm (NT) continued at least one NRTI from their failing regimen; 56% versus 19% were prescribed didanosine+stavudine as their NRTI backbone. Adjusting for baseline HIV-1 RNA, mean reductions in HIV-1 RNA at 48 weeks were 1.51 log₁₀ copies/ml in the RT arm and 1.23 in the NT arm (P = 0.3); the difference between the arms was smaller at week 96 (RT: 1.50, NT: 1.47; P = 0.9). **CONCLUSION:** In this first paediatric trial of resistance testing, we observed a substantial difference in NRTI-prescribing behaviour across arms. However statistically significant evidence of a long-term virological or immunological benefit was not observed. This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN14367816.

Prevention of parent to child transmission

J Infect Dis. 2007 Jul 1;196(1):15-22. Epub 2007 May 16.

Effects of nevirapine, compared with lamivudine, on lipids and lipoproteins in HIV-1-uninfected newborns: the stopping infection from mother-to-child via breast-feeding in Africa lipid substudy.

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BACKGROUND: The objective of the present study was to assess whether the high-density lipoprotein cholesterol (HDL-c)-increasing effect of nevirapine (NVP), as observed in human immunodeficiency virus type 1 (HIV-1)-infected subjects, at least in part may relate to intrinsic properties of NVP. **METHODS:** At 2, 6, and 12 weeks after birth, complete lipid profiles as well as plasma apolipoproteins levels were assessed in 80 HIV-uninfected newborns, half of whom received NVP and half lamivudine (3TC), respectively. Newborns were randomly selected from a randomized trial in which NVP or 3TC had been administered to HIV-uninfected infants born to HIV-infected mothers to try and prevent HIV-1 transmission from occurring during breast-feeding. **RESULTS:** After 6 weeks of therapy, the expected physiological decline in HDL-c levels in the newborns was attenuated in infants treated with NVP, compared with levels in

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those treated with 3TC. Apolipoprotein A-I (apoA-I) levels were higher at all time points in the NVP arm than they were in the 3TC arm ($P=.02$), reaching peak levels at 6 weeks. The difference in HDL-c was no longer significant at 12 weeks. **CONCLUSIONS:** apoA-I levels and HDL-c were elevated in HIV-1-uninfected newborns receiving NVP, compared with those receiving 3TC. These data support that NVP may indeed have intrinsic apoA-I and HDL-c elevating properties in humans.

Clin Infect Dis. 2007 Jan 1;44(1):111-9. Epub 2006 Nov 22.

A randomized, double-blind, placebo-controlled trial of combined nevirapine and zidovudine compared with nevirapine alone in the prevention of perinatal transmission of HIV in Zimbabwe.

Thistle P, Spitzer RF, Glazier RH, Pilon R, Arbess G, Simor A, Boyle E, Chitsike I, Chipato T, Gottesman M, Silverman M.

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BACKGROUND: A single dose of nevirapine (sdNVP) administered to both mother and infant can decrease mother-to-child transmission of human immunodeficiency virus (HIV) by 47%, compared with ultra-short course zidovudine therapy (usZDV). There is limited data about the benefit of usZDV added to sdNVP to prevent mother-to-child transmission. **METHODS:** We performed a double-blind, randomized, placebo-controlled trial to determine whether usZDV combined with sdNVP improved neonatal outcome, compared with sdNVP alone. Mothers were randomized to 1 of 2 treatment groups. Mothers in the usZDV/sdNVP group received a loading dose of zidovudine (600 mg administered orally) and continued to receive 300-mg doses of zidovudine orally every 3 h while in labor, and their infants received zidovudine at a dosage of 2 mg per kg of body weight 4 times per day orally for 72 h. Mothers and infants in the sdNVP group received zidovudine placebo dosed in the same manner. All mothers also received nevirapine at a dosage of 200 mg orally while in labor, and all infants received nevirapine 2 mg per kg of body weight orally within 72 h of delivery. **RESULTS:** The study was stopped on the basis of futility, because interim data showed that, at present trends, superiority would not be demonstrated. Results at 6 weeks of age were available for 609 infants. The primary end point of HIV RNA positivity or death occurred in 21.8% of infants in the usZDV/sdNVP arm and 23.6% of the infants in the sdNVP arm. **CONCLUSION:** usZDV, when added to a standard 2-dose regimen of sdNVP, did not demonstrate a clinically important decrease in the combined end point of mother-to-child transmission or infant death. High rates of adverse maternal and infant outcome in both study arms suggest that improved approaches are necessary.

Am J Clin Nutr. 2006 Sep;84(3):610-5.

Synergy between mannose-binding lectin gene polymorphisms and supplementation with vitamin A influences susceptibility to HIV infection in infants born to HIV-positive mothers.

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BACKGROUND: Mannose-binding lectin (MBL-2) allele variants are associated with deficiencies in innate immunity and have been found to be correlated with HIV infection in adults and children. **OBJECTIVE:** We tested whether MBL-2 variants among infants born to HIV-positive mothers have an increased susceptibility to HIV. **DESIGN:** MBL-2 allele variants were measured among 225 infants born to HIV-positive mothers enrolled in a trial in Durban, South Africa. Mothers of 108 infants were randomly assigned to receive vitamin A and beta-carotene supplementation and 117 to receive placebo. Infants were followed with regular HIV tests to determine rates of mother-to-child HIV transmission. **RESULTS:** A high proportion of infants were either homozygous (10.7%) or heterozygous (32.4%) for MBL-2 variants. MBL-2 variants within the placebo arm were associated with an increased risk of HIV transmission (odds ratio: 3.09; 95% CI: 1.21, 7.86); however, MBL-2 variants within the supplementation arm were not associated with an increased risk of transmission ($P = 0.04$; test of interaction). Among infants with MBL-2 variants, supplementation was associated with a decreased risk of HIV transmission (odds ratio: 0.37; 95% CI: 0.15, 0.91). **CONCLUSION:** We observed what appears to be a gene-environment interaction between MBL-2 variants and an intervention with vitamin A plus beta-carotene that is relevant to mother-to-child HIV transmission.

JAMA. 2006 Aug 16;296(7):794-805.

<http://jama.ama-assn.org/cgi/content/full/296/7/794>

Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study.

Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, Gilbert PB, Stevens L, Peter T, Kim S, van Widenfelt E, Moffat C, Ndase P, Arimi P, Kebaabetswe P, Mazonde P, Makhema J, McIntosh K, Novitsky V, Lee TH, Marlink R, Lagakos S, Essex M; Mashi Study Team.

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CONTEXT: Postnatal transmission of human immunodeficiency virus-1 (HIV) via breastfeeding reverses gains achieved by perinatal antiretroviral interventions. **OBJECTIVE:** To compare the efficacy and safety of 2 infant feeding strategies for the prevention of postnatal mother-to-child HIV transmission. **DESIGN, SETTING, AND PATIENTS:** A 2 x 2 factorial randomized clinical trial with peripartum (single-dose nevirapine vs placebo) and postpartum infant feeding (formula vs breastfeeding with infant zidovudine prophylaxis) interventions. In Botswana between March 27, 2001, and October 29, 2003, 1200 HIV-positive pregnant women were randomized from 4 district hospitals. Infants were evaluated at birth, monthly until age 7 months, at age 9 months, then every third month through age 18 months. **INTERVENTION:** All

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of the mothers received zidovudine 300 mg orally twice daily from 34 weeks' gestation and during labor. Mothers and infants were randomized to receive single-dose nevirapine or placebo. Infants were randomized to 6 months of breastfeeding plus prophylactic infant zidovudine (breastfed plus zidovudine), or formula feeding plus 1 month of infant zidovudine (formula fed). MAIN OUTCOME MEASURES: Primary efficacy (HIV infection by age 7 months and HIV-free survival by age 18 months) and safety (occurrence of infant adverse events by 7 months of age) end points were evaluated in 1179 infants. RESULTS: The 7-month HIV infection rates were 5.6% (32 infants in the formula-fed group) vs 9.0% (51 infants in the breastfed plus zidovudine group) ($P = .04$; 95% confidence interval for difference, -6.4% to -0.4%). Cumulative mortality or HIV infection rates at 18 months were 80 infants (13.9%, formula fed) vs 86 infants (15.1% breastfed plus zidovudine) ($P = .60$; 95% confidence interval for difference, -5.3% to 2.9%). Cumulative infant mortality at 7 months was significantly higher for the formula-fed group than for the breastfed plus zidovudine group (9.3% vs 4.9%; $P = .003$), but this difference diminished beyond month 7 such that the time-to-mortality distributions through age 18 months were not significantly different ($P = .21$). CONCLUSIONS: Breastfeeding with zidovudine prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission, but was associated with a lower mortality rate at 7 months. Both strategies had comparable HIV-free survival at 18 months. These results demonstrate the risk of formula feeding to infants in sub-Saharan Africa, and the need for studies of alternative strategies. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00197587.

Comment

A very important study showing that although formula feeding is associated with lower risk of mother-to-child HIV transmission, it was associated with a higher mortality in Botswana. Other studies of parent-to-child transmission this year showed that routine antibiotics were ineffective in prevention; and adding zidovudine to nevirapine for the mother and baby in Zimbabwe had no additional beneficial effect.

AIDS. 2006 Jun 12;20(9):1313-21.

A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission.

Taha TE, Brown ER, Hoffman IF, Fawzi W, Read JS, Sinkala M, Martinson FE, Kafulafula G, Msamanga G, Emel L, Adeniyi-Jones S, Goldenberg R.

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OBJECTIVE: A multisite study was conducted in Africa to assess the efficacy of antibiotics to reduce mother-to-child transmission (MTCT) of HIV-1. DESIGN: A randomized, double-blinded, placebo-controlled, phase III clinical trial. METHODS: HIV-1-infected women were randomly assigned at 20-24 weeks' gestation to receive either antibiotics (metronidazole plus erythromycin antenatally and metronidazole plus ampicillin intrapartum) or placebo. Maternal study procedures were performed at 20-24, 26-30, and 36 weeks antenatally, and at labor/delivery. Infants were seen at birth, 4-6 weeks, and 3, 6, 9 and 12 months. The primary efficacy endpoints were overall infant HIV-1 infection and HIV-1-free survival at 4-6 weeks. All women and infants received single-dose nevirapine prophylaxis in this study. RESULTS: A total of 1510 live-born infants were included in the primary analysis. The proportions of HIV-1-

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infected infants at birth were similar (antibiotics 7.1%; placebo 8.3%; $P = 0.41$). Likewise, there were no statistically significant differences at 4-6 weeks in the overall risk of MTCT of HIV-1 (antibiotics 16.2%; placebo 15.8%; $P = 0.89$) or HIV-1-free survival (79.4% in each study arm). Post-randomization, the proportion of women with bacterial vaginosis at the second antenatal visit was significantly lower in the antibiotics arm compared with the placebo arm (23.8 versus 39.7%; $P < 0.001$), but the frequency of histological chorioamnionitis was not different (antibiotics 36.9%; placebo 39.7%; $P = 0.30$). Adverse events in mothers and their infants did not differ by randomization arm. **CONCLUSION:** This simple antepartum and peripartum antibiotic regimen did not reduce the risk of MTCT of HIV-1.

Nutrition and development in children with HIV

Am J Clin Nutr. 2007 May;85(5):1335-43.

Multivitamin supplementation improves hematologic status in HIV-infected women and their children in Tanzania.

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BACKGROUND: Anemia is a frequent complication among HIV-infected persons and is associated with faster disease progression and mortality. **OBJECTIVE:** We examined the effect of multivitamin supplementation on hemoglobin concentrations and the risk of anemia among HIV-infected pregnant women and their children. **DESIGN:** HIV-1-infected pregnant women ($n = 1078$) from Dar es Salaam, Tanzania, were enrolled in a double-blind trial and provided daily supplements of preformed vitamin A and beta-carotene, multivitamins (vitamins B, C, and E), preformed vitamin A and beta-carotene + multivitamins, or placebo. All women received iron and folate supplements only during pregnancy according to local standard of care. The median follow-up time for hemoglobin measurement for mothers was 57.3 mo [interquartile range (IQR): 28.6-66.8] and for children it was 28.0 mo (IQR: 5.3-41.7). **RESULTS:** During the whole period, hemoglobin concentrations among women who received multivitamins were 0.33 g/dL higher than among women who did not receive multivitamins ($P=0.07$). Compared with placebo, multivitamin supplementation resulted in a hemoglobin increase of 0.59 g/dL during the first 2 y after enrollment ($P=0.0002$). Compared with placebo, the children born to mothers who received multivitamins had a reduced risk of anemia. In this group, the risk of macrocytic anemia was 63% lower than in the placebo group (relative risk: 0.37; 95% CI: 0.18, 0.79; $P=0.01$). **CONCLUSION:** Multivitamin supplementation provided during pregnancy and in the postpartum period resulted in significant improvements in hematologic status among HIV-infected women and their children, which provides further support for the value of multivitamin supplementation in HIV-infected adults.

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Am J Trop Med Hyg. 2007 Jun;76(6):1066-71.

Effects of maternal vitamin supplements on malaria in children born to HIV-infected women.

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Vitamin deficiencies are frequent in children suffering from malaria. The effects of maternal multivitamin supplementation on the risk of malaria in children are unknown. We examined the impact of providing multivitamins or vitamin A/beta-carotene supplements during pregnancy and lactation to HIV-infected women on their children's risk of malaria up to 2 years of age, in a randomized, placebo-controlled trial. Tanzanian women (N = 829) received one of four daily oral regimens during pregnancy and after delivery: 1) vitamins B, C, and E (multivitamins); 2) vitamin A and beta-carotene (VA/BC); 3) multivitamins including VA/BC; or 4) placebo. After 6 months of age, all children received 6-monthly oral vitamin A supplements irrespective of treatment arm. The incidence of childhood malaria was assessed through three-monthly blood smears and at monthly and interim clinic visits from birth to 24 months of age. Compared with placebo, multivitamins excluding VA/BC reduced the incidence of clinical malaria by 71% (95% CI = 11-91%; P = 0.02), whereas VA/BC alone resulted in a nonsignificant 63% reduction (95% CI = -4% to 87%; P = 0.06). Multivitamins including VA/BC significantly reduced the incidence of high parasitemia by 43% (95% CI = 2-67%; P = 0.04). The effects did not vary according to the children's HIV status. Supplementation of pregnant and lactating HIV-infected women with vitamins B, C, and E might be a useful, inexpensive intervention to decrease the burden of malaria in children born to HIV-infected women in sub-Saharan Africa.

IMCI

Trop Doct. 2007 Apr;37(2):75-9.

Care takers' recall of Integrated Management of Childhood Illness counselling messages in Benin.

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A key goal of the Integrated Management of Childhood Illness (IMCI) strategy is to improve the management of childhood illness at health facilities. IMCI guidelines contain many counselling messages, and as it is not known how well caretakers recall these messages, we studied caretakers' recall of IMCI messages when given under ideal conditions. At a clinic in Benin, a study clinician performed counselling and confirmed caretakers' comprehension of all messages. Caretakers were randomly assigned to be interviewed either immediately after the consultation or a day later. Recall was assessed with general and focused open-ended questions. Recall was assessed for 55 caretakers, 29.1% of whom were literate. Caretakers received 3-75 messages

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(mean = 38.7). The mean percentage of messages recalled was 89.7% immediately after the consultation and 81.9% one day later. These results support IMCI's recommendation that health workers should verify caretakers' comprehension by asking caretakers to repeat counselling messages during consultations.

Iodine deficiency

Am J Clin Nutr. 2006 Nov;84(5):1208-14.

Efficacy of oral iodized peanut oil is greater than that of iodized poppy seed oil among Indonesian schoolchildren.

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BACKGROUND: Oral iodized poppy seed oil is an appropriate measure for controlling iodine deficiency in areas where iodized salt is not yet available. However, a more effective and cheaper iodized oil preparation is needed. **OBJECTIVE:** The aim of this study was to compare the efficacy of iodized peanut oil with that of iodized poppy seed oil. **DESIGN:** Schoolchildren aged 8-10 y were supplemented with a single oral dose of iodized peanut oil (P200, P400, or P800 mg I), iodized poppy seed oil (PS400 mg I), or peanut oil (placebo). The concentration of urinary iodine (UI) was measured at 0, 4, 12, 25, and 50 wk, whereas thyroid volume and serum thyrotropin and free thyroxine concentrations were measured at 0, 25, and 50 wk. **RESULTS:** UI was higher in all treatment groups than in the placebo group, except at baseline. UI in the P200 group was not significantly different from that in the PS400 group at all times of measurement. In a comparison of preparations supplying 400 mg I conducted by using a mathematical model, iodine retention from the peanut oil preparation was 3 times that from the poppy seed oil, and the protection period for peanut oil was twice as long as that for the poppy seed oil ($P < 0.001$ for both). The reduction in thyroid volume was greater in the treatment groups than in the placebo group ($P < 0.001$). No significant differences in serum hormone concentrations were observed between groups before or after treatment. **CONCLUSION:** Iodized peanut oil is more efficacious in controlling iodine deficiency than is iodized poppy seed oil containing the same amount of iodine.

J Nutr. 2006 Jul;136(7):1814-20.

<http://jn.nutrition.org/cgi/content/full/136/7/1814>

Salt dual-fortified with iodine and micronized ground ferric pyrophosphate affects iron status but not hemoglobin in children in Cote d'Ivoire.

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Deficiencies of iron and iodine are common in West Africa, and salt is one of very few food vehicles available for fortification. Salt dual-fortified with iodine and micronized ground ferric pyrophosphate (FePP) was tested for its efficacy in rural, tropical Côte d'Ivoire. First, salt and iron intakes, and iron bioavailability were estimated using 3-d weighed food records in 24 households. Local iodized salt was then fortified with 3 mg Fe/g salt as ground FePP (mean particle size = 2.5 µm), and stability, sensory and acceptability trials were done. The dual fortified salt (DFS) was distributed to households and its efficacy compared with that of iodized salt (IS) in a 6-mo, double-blind trial in 5- to 15-y-old iron-deficient children (n = 123). All children were dewormed at baseline. After 6 mo, serum ferritin (SF) and transferrin receptor (TfR) concentrations as well as body iron stores improved significantly in the DFS group but not in the IS GROUP (P < 0.05). Body iron increased from 4.6 +/- 2.7 to 5.9 +/- 2.7 mg/kg (mean +/- SD) in the DFS group; concentrations before and after treatment in the IS group were 5.5 +/- 2.9 and 5.6 +/- 3.1 mg/kg, respectively. The hemoglobin concentration and the prevalence of anemia did not change in either group. The prevalences of malaria, soil-transmitted helminths, and riboflavin deficiency were 55, 14, and 66%, respectively. In tropical West Africa, low-grade salt fortified with micronized ground FePP increased body iron stores but not hemoglobin in children. Iron utilization may have been impaired by the high prevalence of malaria and concurrent nutrient deficiencies.

Iron deficiency

(See also Vitamin A, Malaria and Development)

Am J Trop Med Hyg. 2006 Jul;75(1):126-32.

<http://www.ajtmh.org/cgi/content/full/75/1/126>

Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon.

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Iron and zinc deficiencies are common in developing countries and supplementation is one way of reversing these deficiencies. The objective of this randomized, placebo-controlled clinical trial was to identify the effect of daily supplementation with iron, zinc, and iron plus zinc on the morbidity experience of 855 children 0.5-15 years of age in Peru. Single nutrient supplementation with zinc reduced diarrhea morbidity by 23% in all children. In older children (more than five years of age), iron supplementation increased morbidity due to *Plasmodium vivax* and diarrhea. In younger children, iron combined with zinc provided protection against *P. vivax* malaria, but also interfered with some of the diarrhea protection associated with zinc supplementation. No statistically significant effect was observed of either supplement on incidence of respiratory infection or anthropometric indices. Iron and zinc deficiencies should be remedied, and combined supplementation may be a good option, particularly in younger children in *P. vivax* malaria-endemic areas, although local endemicity and species-specific

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prevalence should be considered carefully when designing any supplementation program involving iron in a malaria-endemic area.

Comment

This important study emphasizes the potential dangers of iron supplementation in malaria endemic areas (also shown last year in Lancet. 2006;367:133-43). This current study showed that iron increased the risk of vivax malaria in children over the age of 5 years, and increased the risk of diarrhoea. This trial administered 15mg iron daily. Interestingly, another trial published this year from India of iron (9.6mg per day) and zinc fortification of milk in India showed a reduction in episodes of diarrhoea, compared to children given unfortified milk (see Nutrition, study by Sazawal S, et al. BMJ. 2007;334:140. Epub 2006 Nov 28).

Food Nutr Bull. 2006 Sep;27(3):260-4.

Nutrition education alone improves dietary practices but not hematologic indices of adolescent girls in Iran.

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BACKGROUND: Iron-deficiency anemia is the most prevalent nutritional deficiency worldwide. Iron-deficiency anemia has particular negative consequences on women in their childbearing years, and its prevention is a high priority in most health systems. **OBJECTIVE:** This interventional study assessed the effect of nutrition education on hematologic indices, iron status, nutritional knowledge, and nutritional practices of high-school girls in Iran. **METHODS:** Sixty healthy 16- to 18-year-old girls were randomly selected from two high schools in the city of Ahvaz and divided into two equally matched groups, one that received nutrition education, and one that did not. The education group received instruction in face-to-face sessions, group discussions, and pamphlets for 2 months. The control group did not receive any information during the study. Hematologic tests, corpuscular indices, and serum ferritin levels were measured at baseline and after 2 months. Food-frequency questionnaires were administered and histories taken, clinical signs of nutritional deficiencies observed, anthropometric measurements taken, nutritional knowledge tested, practices determined, and lifestyle questionnaires administered to all subjects. **RESULTS:** There were no statistically significant differences in any baseline characteristics between the two groups. Scores for nutritional knowledge and practices of the education group were significantly higher after two months compared with the baseline (31.4 +/- 6 vs. 24.3 +/- 5.9 points, $p < .001$, and 31.2 +/- 5 vs. 28.4 +/- 5.7 points, $p < .05$, respectively). The scores in the control group showed no significant changes from baseline to 2 months. Mean corpuscular volume values were elevated in the education group ($p < .001$) but not in the control group. However, in the control group, serum ferritin concentrations showed about a 17% drop at the end of the study ($p < .004$). There were no changes in other hematologic, lifestyle, clinical, or anthropometric data compared with baseline after completion of the study in both groups. **CONCLUSION:** These findings indicate that nutritional education can improve knowledge of healthy nutrition and lifestyle choices. Focused nutritional education using available resources and correcting current dietary habits in a vulnerable group of young women may result in dietary changes that can ultimately improve iron intake.

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Food Nutr Bull. 2006 Sep;27(3):220-7.

Effectiveness of intermittent iron treatment of two- to six-year-old Jordanian children with iron-deficiency anemia.

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BACKGROUND: Iron deficiency is a common nutritional problem in young children among vulnerable populations in Jordan. Several studies have shown the effectiveness of intermittent iron supplementation in improving iron status. Such a study has not been carried out in 2- to 6-year-old Jordanian children diagnosed with iron deficiency anemia in a clinical setting.

OBJECTIVE: To study the effectiveness of intermittent versus daily iron treatment in a clinical setting in 2- to 6-year-old Jordanian children with iron-deficiency anemia. **METHODS:** About 4400 children aged 2 to 6 years who visited Prince Hashim Military Hospital in Zarqa, Jordan, from August 2000 to June 2001 were screened for age, general health, and birthweight. About 10% of these children were screened for anemia, using complete blood count (defined as a hemoglobin level $< \text{or} = 10.5 \text{ g/dL}$, and a mean corpuscular volume $< \text{or} = 75 \text{ fL}$). Anemic children underwent further screening for iron deficiency, defined as serum ferritin level $< \text{or} = 12 \text{ microg/L}$. Children with iron-deficiency anemia, as indicated by hemoglobin $< \text{or} = 10.5 \text{ g/dL}$, mean corpuscular volume $< \text{or} = 75 \text{ fL}$, and serum ferritin $< \text{or} = 12 \text{ microg/L}$, or as indicated by mean corpuscular volume $< \text{or} = 75 \text{ fL}$ and hemoglobin $< \text{or} = 10.5 \text{ g/dL}$, were enrolled in the study after informed oral consent by their parents. Study children ($n=134$) were assigned randomly to one of three groups. Subjects in group 1 ($n=45$), group 2 ($n=45$), and group 3 ($n=44$) received iron treatment daily, weekly, and twice weekly, respectively. Out of 134 children recruited for the study, only 63 (39 boys and 24 girls) completed the 3-month treatment period. All of the children received medicinal iron drops at a dosage of 5 mg elemental iron as ferrous sulfate per kilogram of body weight. The parents also received nutritional counseling. **RESULTS:** At the end of treatment, hemoglobin, serum ferritin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration increased significantly in all groups with no significant differences between groups. The increases in hemoglobin in groups 1, 2, and 3 were 2.47 ± 0.17 , 2.12 ± 0.18 , and $2.18 \pm 0.18 \text{ g/dL}$, respectively. Measurements of final serum ferritin concentration were available for only 12, 12, and 10 children in groups 1, 2, and 3, respectively. In all children who completed the study, except for one in group 1, hemoglobin, mean corpuscular volume, and serum ferritin reached normal values in response to iron treatment. **CONCLUSIONS:** Weekly and twice-weekly iron therapy with 5 mg elemental iron as ferrous sulfate per kilogram of body weight accompanied by nutritional counseling was as effective as daily iron therapy in correcting iron-deficiency anemia in 2- to 6-year-old children under the clinical conditions of this study.

Lancet. 2007 May 26;369(9575):1799-806.

Efficacy of iron-fortified whole maize flour on iron status of schoolchildren in Kenya: a randomised controlled trial.

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BACKGROUND: Sodium iron edetic acid (NaFeEDTA) might be a more bioavailable source of iron than electrolytic iron, when added to maize flour. We aimed to assess the effect, on children's iron status, of consumption of whole maize flour fortified with iron as NaFeEDTA or electrolytic iron. **METHODS:** 516 children, aged 3-8 years, from four schools in Marafa, Kenya, were randomly assigned to four groups. All were given the same amount of porridge five times a week. The porridge for one group was made from unfortified whole maize flour; for the other three groups it was fortified with either high-dose NaFeEDTA (56 mg/kg), low-dose NaFeEDTA (28 mg/kg), or electrolytic iron (56 mg/kg). Concentrations of haemoglobin, plasma ferritin, and transferrin receptor were analysed in samples taken at baseline and at the end of the 5-month intervention. The primary outcome was iron-deficiency anaemia. We analysed data on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT00386074. **FINDINGS:** The prevalence of iron-deficiency anaemia in children given unfortified flour was 10%. Compared with placebo, the prevalence of iron-deficiency anaemia in children given flour fortified with high-dose NaFeEDTA, low-dose NaFeEDTA, and electrolytic iron changed by -89% (95% CI -97% to -49%), -48% (-77% to 20%), and 59% (-18% to 209%), respectively. Consumption of high-dose NaFeEDTA improved all measured iron-status indicators. Low-dose NaFeEDTA decreased the prevalence of iron deficiency but did not noticeably change the prevalence of anaemia. Electrolytic iron did not improve any of these iron-status indicators. Children who were iron-deficient at baseline benefited more from high-dose and low-dose NaFeEDTA than those with sufficient iron at baseline. **INTERPRETATION:** Consumption of whole maize flour fortified with NaFeEDTA caused modest, dose-dependent improvements in children's iron status. Fortification with electrolytic iron did not improve their iron status. Therefore, in high-phytate flours, NaFeEDTA is more suitable than electrolytic iron for supplementation of iron in the diet.

Indian Pediatr. 2007 Feb;44(2):91-100.

<http://www.indianpediatrics.net/feb2007/91.pdf>

Low dose 'Sprinkles'-- an innovative approach to treat iron deficiency anemia in infants and young children.

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Iron supplementation programs using pediatric tablets or drops have not been successful in the control of anemia amongst infants and children in India. Sprinkles is an innovative multi-micronutrient home fortification strategy to control iron deficiency and anemia. **OBJECTIVE:** We aimed to determine the hematologic response to different doses and forms of iron in Sprinkles and iron drops. **SETTING:** Twenty two villages of Vadu Rural Health Program, KEM Hospital, Pune. **DESIGN:** Double blind clustered randomized community-based trial. **SUBJECTS:** Children (n=432) aged 6 to 18 mo age with Hb between 70 to 100 g/L were

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enrolled. METHODS: Selected villages were randomized into 5 groups: Sprinkles 12.5, 20 or 30 mg ferrous fumarate, Sprinkles 20 mg micronized ferric pyrophosphate or drops 20 mg ferrous glycine sulphate (DROPS) for 8 weeks. Household socio-demographic information was collected at baseline. Side effects and compliance were monitored through weekly visits. Hemoglobin was estimated at baseline, 3 and 8 weeks. Ferritin was assessed at baseline and 8 weeks. RESULTS: Baseline characteristics were similar across all groups. Hemoglobin increased significantly ($P < 0.0001$) in all groups at 8 weeks with no difference between groups. Ferritin increased ($P < 0.0001$) significantly in all groups with no difference across the groups. Compliance (overall range: 42 to 62 %) was lowest for DROPS. Side effects were significantly higher among DROPS compared to Sprinkles ($p > 0.05$). CONCLUSIONS: Sprinkles 12.5 mg FF dose is as efficacious as higher doses of iron in Sprinkles or DROPS in increasing hemoglobin. Sprinkles FF 12.5 mg is recommended as it has fewer reported side effects and better compliance compared to DROPS.

Comment

Studies of iron supplementation need to be large enough to examine for increased morbidity

Matern Child Nutr. 2006 Jul;2(3):169-80.

Multi-micronutrient Sprinkles including a low dose of iron provided as microencapsulated ferrous fumarate improves haematologic indices in anaemic children: a randomized clinical trial.

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Home-fortification of complementary foods with micronutrients (including iron) as Sprinkles is a new strategy to control iron deficiency and anaemia in developing countries. However, the most effective dose and form of iron is not known. The purpose of this study was to compare the efficacy of various doses (12.5, 20 or 30 mg) and treatment methods (multi-micronutrient Sprinkles vs. ferrous sulphate drops) on haemoglobin (Hb) concentration after 8 weeks of treatment in anaemic children. In total, 133 anaemic Ghanaian children (Hb 70-99 g L⁻¹) aged 6-18 months were randomly assigned to one of five daily interventions for 8 weeks. Out of the five interventions, four used Sprinkles, and one used iron drops. Of the four Sprinkles groups, three included 12.5, 20 or 30 mg of iron as ferrous fumarate, and one included 20 mg of iron as ferric pyrophosphate. The iron drops group included 12.5 mg of iron as liquid ferrous sulphate. Hb concentrations were measured at baseline, week 3 and week 8. The primary outcome measure was Hb concentration at 8 weeks after treatment. We compared differences in Hb and ferritin concentrations and prevalence of iron deficiency anaemia (Hb < 100 g L⁻¹) and soluble transferrin receptor concentrations >8.5 mg L⁻¹) from baseline to 8 weeks within and between groups. Adherence and reporting of side effects (staining of the teeth, ease of use, diarrhoea and darkening of stools) were compared between groups. Mean change in Hb was 1.4 g L⁻¹ (SD = 1.8) ($P = 0.0001$). Change in Hb concentrations from baseline to 8 weeks was significant in all

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groups ($P = 0.0001-0.0007$), with no differences across groups. Geometric means of serum ferritin varied from 18.6 to 44.0 microg L(-1) at baseline. At week 8, these means were in the interval of 48.0-78.3 microg L(-1), with no group differences. Prevalence of iron deficiency anaemia decreased significantly from baseline to 8 weeks in all groups with the exception of the iron drops group, with no group differences. Adherence was lower in the drops group (64%) as compared with Sprinkles groups (84%). Greater staining of the teeth and less ease of use were reported in the drops group as compared with Sprinkles groups. A dose as low as 12.5 mg of iron as ferrous fumarate when provided as Sprinkles may be effective in anaemic children.

Asia Pac J Clin Nutr. 2007;16(1):116-21.

Effects of wheat flour fortified with different iron fortificants on iron status and anemia prevalence in iron deficient anemic students in Northern China.

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OBJECTIVES: To compare the effects of wheat flours fortified with NaFeEDTA, FeSO₄ and elemental iron (electrolytic iron), in improving iron status in anemic students. **METHODS:** Four hundreds anemic students (11 to 18 years old) were divided into four groups and given wheat flour fortified with different iron fortificants at different concentrations: control group (no added iron); NaFeEDTA group (20 mg Fe/kg); FeSO₄ group (30 mg Fe/kg); and elemental iron group (60 mg Fe/kg). The trial lasted for 6 months and the following parameters were examined every 2 months: whole blood hemoglobin, free erythrocyte protoporphyrin, serum ferritin, serum iron, total iron binding capacity and transferrin receptor. **RESULTS:** The flour consumption in the 4 groups was 300-400 g/person/day, accounted for 70% of total cereal consumption in the diets. There were no significant differences in flour consumption among the 4 groups. Blood hemoglobin level increased in all the 3 intervened groups, but the increment in the NaFeEDTA group was significantly higher and earlier than the other 2 groups; and only 1% of the subjected remained anemic at the end of the trial in the NaFeEDTA group, while 40% and 60% of the subjects in the FeSO₄ and electrolytic iron group remained anemic, respectively. The order of improvements in free erythrocyte protoporphyrin, serum ferritin and transferrin receptor levels were: NaFeEDTA > FeSO₄ > electrolytic iron. No significant changes were found in the control group on all the tested parameters during the trial. **CONCLUSIONS:** The results indicated that even NaFeEDTA was added at a lower level, it has better effects than FeSO₄ and elemental iron on controlling iron deficiency anemia and improving iron status in anemic children; while elemental iron was the least effective.

J Egypt Public Health Assoc. 2005;80(5-6):525-45.

Health education program for mothers of children suffering from iron deficiency anemia in United Arab Emirates.

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The present study was designed to assess knowledge, beliefs and practices of mothers regarding factors leading to iron deficiency anemia among children, to develop a health education (HE) program according to the needs of the target group, to determine the effect of the program in terms of changes in mothers' knowledge, practices and beliefs using Health Belief Model (HBM), and to determine the hemoglobin and hematocrite levels of the children of the target group before and after the program. The sample size was 200 anemic children aged 6-24 months and their mothers, 100 of them were randomly assigned to face to face intervention program (experimental group) (I), the other 100 were the control group (II). Only 16% of mothers of group I and 18% of mothers of group II got satisfactory level of knowledge. After the conduction of HE program, the mothers' knowledge was significantly increased among group I, while almost there was no change of the knowledge's level among group II. Only 7% of mothers of group I and 27% of those of group II had high perceived severity. Only 8% of mothers of group I and 14% of those of group II had low perceived barriers. After the program, 58% of mothers in group I got low perceived barriers. Only 28% of mothers of group I and 21% of those of group II had good dietary practice. After the program, 74% of mothers in group I showed good dietary practice. There were highly significant increases in the levels of hemoglobin and hematocrite of children of group I after the program, while the increases were not significant in group II.

Br J Nutr. 2006 Dec;96(6):1134-9.

Levels of serum transferrin receptor and its response to Fe-supplement in Fe-deficient children.

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The object of the present study was to investigate the levels of serum transferrin receptor (sTfR) and its response to Fe supplementation in Fe-deficient children and the role of sTfR in detecting Fe deficiency and assessing the efficacy of Fe supplementation. According to the diagnostic standard, 1006 children, aged 6-14 years in Fangshan district, Beijing, Peoples Republic of China, were divided into four groups: normal; Fe store depletion (IDs); Fe deficiency erythropoiesis (IDE); Fe deficiency anaemia (IDA). sTfR was determined and transferrin receptor-ferritin (TfR-F) index was calculated in 238 children, sixty-four normal and 174 Fe deficient. Children were administered a NaFeEDTA capsule containing 60 mg Fe once per week for the IDs and IDE groups and three times per week for the IDA group for nine consecutive weeks. The parameters reflecting Fe status and sTfR were determined before and after Fe supplementation. The levels of sTfR and TfR-F index in Fe-deficient children were significantly higher than those in the normal group. The receiver operating characteristic curve showed that sTfR has proper diagnostic efficacy for functional Fe deficiency. After Fe supplementation, the level of sTfR was significantly decreased in children with IDs, but not in children with IDE and

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IDA, while TfR-F index was significantly decreased in Fe-deficient children. sTfR is a reliable indicator for detecting functional Fe deficiency, and TfR-F index is a sensitive parameter for assessing the efficacy of Fe supplementation.

Nutr J. 2006 Dec 5;5:32.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17147795>

Efficacy of iron fortification compared to iron supplementation among Vietnamese schoolchildren.

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The effect of iron fortification is generally assumed to be less than iron supplementation; however, the magnitude of difference in effects is not known. The present study aims to compare the efficacy of these two strategies on anaemia and iron status. After screening on low Hb, 425 anaemic children in six primary schools in Tam Nong district of Phu Tho province were included in a randomized, placebo-controlled trial comparing two groups receiving iron fortified instant noodles or iron supplementation for 6 months and a control group, with children in all groups having been dewormed. Blood samples were collected before and after intervention for haemoglobin, serum ferritin (SF), serum transferrin receptor (TfR), C-reactive protein (CRP), and haemoglobinopathies analysis. Regression analysis was used to assess the effect of iron fortification and iron supplementation on haemoglobin concentration, SF, TfR, body iron, and anaemic status as outcome variables. The improvement of haemoglobin, SF, and body iron level in the group receiving iron fortification was 42% (2.6 g/L versus 6.2 g/L), 20% (23.5 microg/L versus 117.3 microg/L), and 31.3% (1.4 mg/kg versus 4.4 mg/kg) of that in the iron supplementation group. The prevalence of anaemia dropped to 15.1% in the control group, with an additional reduction of anaemia of 8.5% in the iron supplementation group. The additional reduction due to iron fortification was 5.4%, which amounts to well over 50% of the impact of supplementation. In conclusion, the efficacy of iron fortification based on reduction of prevalence of anaemia, and on the change in haemoglobin level, is about half of the maximum impact of supplementation in case of optimal compliance. Thus, in a population of anaemic children with mild iron deficiency, iron fortification should be the preferred strategy to combat anaemia.

Am J Clin Nutr. 2006 Oct;84(4):822-9.

Extruded rice fortified with micronized ground ferric pyrophosphate reduces iron deficiency in Indian schoolchildren: a double-blind randomized controlled trial.

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BACKGROUND: Iron fortification of rice could be an effective strategy for reducing iron deficiency anemia in South Asia. **OBJECTIVE:** We aimed to determine whether extruded rice grains fortified with micronized ground ferric pyrophosphate (MGFP) would increase body iron stores in children. **DESIGN:** In a double-blind, 7-mo, school-based feeding trial in Bangalore, India, iron-depleted, 6-13-y-old children (n = 184) were randomly assigned to receive either a rice-based lunch meal fortified with 20 mg Fe as MGFP or an identical but unfortified control meal. The meals were consumed under direct supervision, and daily leftovers were weighed. All children were dewormed at baseline and at 3.5 mo. Iron status and hemoglobin were measured at baseline, 3.5 mo, and 7 mo. **RESULTS:** At baseline, the prevalences of iron deficiency and iron deficiency anemia in the total sample were 78% and 29%, respectively. After 7 mo of feeding, there was a significant increase in body iron stores in both study groups ($P < 0.001$), with a greater increase in the iron group than in the control group ($P < 0.05$). There was a significant time x treatment interaction for iron deficiency, which fell from 78% to 25% in the dewormed iron group and from 79% to 49% in the dewormed control group. Iron deficiency anemia decreased from 30% to 15% (NS) in the iron group but remained virtually unchanged in the control group (28% and 27%). In sensory tests, the MGFP-fortified rice (fortified at 3 and 5 mg Fe/100 g) was indistinguishable from natural rice, in both cooked and uncooked form. **CONCLUSIONS:** Extruded rice fortified with MGFP has excellent sensory characteristics. Fed in a school lunch meal, it increases iron stores and reduces the prevalence of iron deficiency in Indian children.

J Nutr. 2006 Sep;136(9):2405-11.

Iron and zinc supplementation improved iron and zinc status, but not physical growth, of apparently healthy, breast-fed infants in rural communities of northeast Thailand.

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Iron deficiency is prevalent in children and infants worldwide. Zinc deficiency may be prevalent, but data are lacking. Both iron and zinc deficiency negatively affect growth and psychomotor development. Combined iron and zinc supplementation might be beneficial, but the potential interactions need to be verified. In a randomized, placebo-controlled trial using 2 x 2 factorial design, 609 Thai infants aged 4-6 mo were supplemented daily with 10 mg of iron and/or 10 mg of zinc for 6 mo to investigate effects and interactions on micronutrient status and growth. Iron supplementation alone increased hemoglobin and ferritin concentrations more than iron and zinc combined. Anemia prevalence was significantly lower in infants receiving only iron than in infants receiving iron and zinc combined. Baseline iron deficiency was very low,

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and iron deficiency anemia was almost nil. After supplementation, prevalence of iron deficiency and iron deficiency anemia were significantly higher in infants receiving placebo and zinc than in those receiving iron or iron and zinc. Serum zinc was higher in infants receiving zinc (16.7 +/- 5.2 micromol/L), iron and zinc (12.1 +/- 3.8 micromol/L) or iron alone (11.5 +/- 2.5 micromol/L) than in the placebo group (9.8 +/- 1.9 micromol/L). Iron and zinc interacted to affect iron and zinc status, but not hemoglobin. Iron supplementation had a small but significant effect on ponderal growth, whereas zinc supplementation did not. To conclude, in Thai infants, iron supplementation improved hemoglobin, iron status, and ponderal growth, whereas zinc supplementation improved zinc status. Overall, for infants, combined iron and zinc supplementation is preferable to iron or zinc supplementation alone.

Leishmaniasis

N Engl J Med. 2007 Jun 21;356(25):2571-81.

Injectable paromomycin for Visceral leishmaniasis in India.

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BACKGROUND: Visceral leishmaniasis (kala-azar) affects large, rural, resource-poor populations in South Asia, Africa, and Brazil. Safe, effective, and affordable new therapies are needed. We conducted a randomized, controlled, phase 3 open-label study comparing paromomycin, an aminoglycoside, with amphotericin B, the present standard of care in Bihar, India. **METHODS:** In four treatment centers for visceral leishmaniasis, 667 patients between 5 and 55 years of age who were negative for the human immunodeficiency virus and had parasitologically confirmed visceral leishmaniasis were randomly assigned in a 3:1 ratio to receive paromomycin (502 patients) at a dose of 11 mg per kilogram of body weight intramuscularly daily for 21 days or amphotericin B (165 patients) at a dose of 1 mg per kilogram intravenously every other day for 30 days. Final cure was assessed 6 months after the end of treatment; safety assessments included daily clinical evaluations and weekly laboratory and audiometric evaluations. Noninferiority testing was used to compare 6-month cure rates, with a chosen margin of noninferiority of 10 percentage points. **RESULTS:** Paromomycin was shown to be noninferior to amphotericin B (final cure rate, 94.6% vs. 98.8%; difference, 4.2 percentage points; upper bound of the 97.5% confidence interval, 6.9; $P < 0.001$). Mortality rates in the two groups were less than 1%. Adverse events, which were more common among patients receiving paromomycin than among those receiving amphotericin B (6% vs. 2%, $P = 0.02$), included transient elevation of aspartate aminotransferase levels (>3 times the upper limit of the normal range); transient reversible ototoxicity (2% vs. 0, $P = 0.20$); and injection-site pain (55% vs. 0, $P < 0.001$); and in patients receiving amphotericin B, as compared with those receiving paromomycin, nephrotoxicity (4% vs. 0, $P < 0.001$), fevers (57% vs. 3%), rigors (24% vs. 0, $P < 0.001$), and vomiting (10% vs. $<1\%$, $P < 0.001$). **CONCLUSIONS:** Paromomycin was shown to be noninferior to amphotericin B for the treatment of visceral leishmaniasis in India. (ClinicalTrials.gov number, NCT00216346.) Copyright 2007 Massachusetts Medical Society.

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Biomedica. 2006 Oct;26 Suppl 1:152-66.

A multifaceted intervention to prevent American cutaneous leishmaniasis in Colombia: results of a group-randomized trial.

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INTRODUCTION: American cutaneous leishmaniasis is endemic in Colombia, where approximately 6.000 new cases are reported every year. Current prevention and control measures are restricted to the diagnosis and treatment of cases. **OBJECTIVE:** To evaluate the efficacy of a multifaceted intervention to prevent the transmission of *Leishmania* in the endemic focus of Tumaco, on the Pacific Coast of Colombia. **MATERIALS AND METHODS:** A group-randomized trial was conducted. Twenty villages were matched according to prevalence of *Leishmania* infection, number of inhabitants and level of community participation, and then randomly assigned to intervention or control. The intervention included deltamethrin-impregnated bednets, repellent (20% diethyltoluamide and 0.5% permethrin), modification of sand fly resting sites, and health education. Villages were under surveillance for one year and the use of the intervention measures monitored. The incidence of American cutaneous leishmaniasis and *Leishmania* infection in the two groups were compared, adherence to the intervention and adverse events were monitored, and the results were adjusted for village intraclass correlation. **RESULTS:** Ten cases of American cutaneous leishmaniasis were confirmed in the intervention and 23 in the control group, OR = 0.42, 95% CI 0.14-1.26. The intervention had a greater effect in children < 10 years old, in people living on the periphery of the village and in villages with a prevalence of infection in small children > 1%. Adverse events associated with the use of the bednets and the repellent were reported in 2% of the participants and were always mild. **CONCLUSION:** Incident cases of American cutaneous leishmaniasis were reduced by 58% in the intervention group. However, the small number of cases renders the effect estimate imprecise and precludes us to claim a protective effect for the intervention. Specific populations could be the targets of simpler and more cost-effective interventions in the future.

Malaria

Malaria vaccine

Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006199.

Vaccines for preventing malaria (blood-stage).

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BACKGROUND: A malaria vaccine is needed because of the heavy burden of mortality and morbidity due to this disease. This review describes the results of trials of blood (asexual)-stage vaccines. Several are under development, but only one (MSP/RESA, also known as Combination B) has been tested in randomized controlled trials. **OBJECTIVES:** To assess the effect of blood-stage malaria vaccines in preventing infection, disease, and death. **SEARCH STRATEGY:** In March 2006, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2006, Issue 1), MEDLINE, EMBASE, LILACS, and the Science Citation Index. We also searched conference proceedings and reference lists of articles, and contacted organizations and researchers in the field. **SELECTION CRITERIA:** Randomized controlled trials comparing blood-stage vaccines (other than SPf66) against *P. falciparum*, *P. vivax*, *P. malariae*, or *P. ovale* with placebo, control vaccine, or routine antimalarial control measures in people of any age receiving a challenge malaria infection. **DATA COLLECTION AND ANALYSIS:** Both authors independently assessed trial quality and extracted data. Results for dichotomous data were expressed as relative risks (RR) with 95% confidence intervals (CI). **MAIN RESULTS:** Five trials of MSP/RESA vaccine with 217 participants were included; all five reported on safety, and two on efficacy. No severe or systemic adverse effects were reported at doses of 13 to 15 microg of each antigen (39 to 45 microg total). One small efficacy trial with 17 non-immune participants with blood-stage parasites showed no reduction or delay in parasite growth rates after artificial challenge. In the second efficacy trial in 120 children aged five to nine years in Papua New Guinea, episodes of clinical malaria were not reduced, but MSP/RESA significantly reduced parasite density only in children who had not been pretreated with an antimalarial drug (sulfadoxine-pyrimethamine). Infections with the 3D7 parasite subtype of MSP2 (the variant included in the vaccine) were reduced (RR 0.38, 95% CI 0.26 to 0.57; 719 participants) while those with the other main subtype, FC27, were not (720 participants). **AUTHORS' CONCLUSIONS:** The MSP/RESA (Combination B) vaccine shows promise as a way to reduce the severity of malaria episodes, but the effect of the vaccine is MSP2 variant-specific. Pretreatment for malaria during a vaccine trial makes the results difficult to interpret, particularly with the relatively small sample sizes of early trials. The results show that blood-stage vaccines may play a role and merit further development.

Trop Med Int Health. 2007 Jan;12(1):37-46.

Safety and immunogenicity of the RTS,S/AS02A candidate malaria vaccine in children aged 1-4 in Mozambique.

Macete E, Aponte JJ, Guinovart C, Sacarlal J, Ofori-Anyinam O, Mandomando I, Espasa M, Bevilacqua C, Leach A, Dubois MC, Heppner DG, Tello L, Milman J, Cohen J, Dubovsky F, Tornieporth N, Thompson R, Alonso PL.

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BACKGROUND: The development of a malaria vaccine remains a public health priority for sub-Saharan Africa. RTS,S/AS02A candidate malaria vaccine has been shown to be safe and immunogenic in previous studies in adults and staggered dose-escalation studies in children in The Gambia. However, genetic features and the intensity of malaria transmission may modify the safety and immune response of a vaccine. **OBJECTIVE:** We carried out a phase I, double-

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blind randomized controlled trial in 60 children aged 1-4 in Mozambique to evaluate the safety, reactogenicity and immunogenicity of the paediatric vaccine dose (fixed 25 microg RTS,S in 0.25 ml) of RTS,S/AS02A, prior to undertaking a planned larger phase IIb proof-of-concept of efficacy study in the same population. **METHOD:** Children were randomized to receive either RTS,S/AS02A or Engerix-B vaccine. Monitoring of safety and reactogenicity included detailed clinical and laboratory analyses and assessment of adverse events (AEs). **RESULTS:** The RTS,S/AS02A was found to be safe and well tolerated. Serious adverse events were balanced between both groups and none was related to vaccination. The frequency of adverse events reported with RTS, S/AS02A was comparable to previous studies in children. Grade 3 AEs were infrequent (one case of pain, one of fever in each group and some swelling greater than 20 mm in diameter), transient and resolved without sequelae. RTS,S/AS02A was highly immunogenic for anti-circumsporozoite protein antibody response and induced a strong anti-hepatitis-B surface antigen response.

Intermittent presumptive treatment

Antimicrob Agents Chemother. 2007 Jul 16; [Epub ahead of print]

Intermittent preventive treatment in infants as a mean of malaria control: a randomized, double-blind, and placebo-controlled trial in northern Ghana.

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Morbidity and mortality from malaria remain unacceptably high among young children in sub-Saharan Africa. Intermittent preventive treatment in infancy (IPTi) involves the administration of antimalarials alongside routine vaccinations and might be an option in malaria control. In an area of intense, perennial malaria transmission in northern Ghana, 1200 children received IPTi with sulfadoxine-pyrimethamine or placebo at approximately 3, 9, and 15 months of age. Children were followed-up until 24 months of age to assess morbidity and adverse events. During the intervention period (3-18 months of age), IPTi reduced the incidences of malaria and severe anemia by 22.5% (95%CI, 12-32%) and 23.6% (4-39%), respectively, and hospitalizations and episodes of asymptomatic parasitemia by one third. Protection was pronounced in the first year of life and not discernible in the second. The malaria-protective effect was largely confined to a period of one month after sulfadoxine-pyrimethamine treatments. Following the intervention, protection against asymptomatic parasitemia persisted. In contrast, a significant rebound of severe malaria, predominantly severe malarial anemia, occurred among children having received IPTi. Generally well tolerated, one case of moderately severe skin reaction followed sulfadoxine-pyrimethamine treatment. IPTi reduces malaria and

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anemia in infants in northern Ghana. Extension of IPTi into the second year of life by administering a dose at 15 months of age provided no substantial benefit beyond a one-month prophylactic effect. Although this simple intervention offers one of the few available malaria-preventive measures for endemic regions, the observed rebound of severe malaria advises caution and requires further investigation.

Comment

This study shows how important it is to follow-up children after IPTi doses have been completed. In this study those receiving IPTi had a subsequent increased risk of severe malaria, a probable rebound effect of delayed acquisition of immunity from prophylaxis in infancy. A recent analysis of the long-term follow-up of a trial of chemoprophylaxis in infants in Tanzania (Aponte, PLoS Med. 2007 31;4:e242) found that while there was a significant impact of chemoprophylaxis on acquisition of immunity and thus a rebound in morbidity following the intervention, the cumulative rates of severe malaria and severe anaemia in the intervention group remained just below those of the control group up until 4 years of age. The results of further IPTi trials are awaited in 2008.

Clin Infect Dis. 2007 Jul 1;45(1):16-25. Epub 2007 May 29.

A randomized controlled trial of extended intermittent preventive antimalarial treatment in infants.

Kobbe R, Kreuzberg C, Adjei S, Thompson B, Langefeld I, Thompson PA, Abruquah HH, Kreuels B, Ayim M, Busch W, Marks F, Amoah K, Opoku E, Meyer CG, Adjei O, May J.

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BACKGROUND: Intermittent preventive antimalarial treatment in infants (IPTi) with sulfadoxine-pyrimethamine reduces falciparum malaria and anemia but has not been evaluated in areas with intense perennial malaria transmission. It is unknown whether an additional treatment in the second year of life prolongs protection. **METHODS:** A randomized, double-blinded, placebo-controlled trial with administration of sulfadoxine-pyrimethamine therapy at 3, 9, and 15 months of age was conducted with 1070 children in an area in Ghana where malaria is holoendemic. Participants were monitored for 21 months after recruitment through active follow-up visits and passive case detection. The primary end point was malaria incidence, and additional outcome measures were anemia, outpatient visits, hospital admissions, and mortality. Stratified analyses for 6-month periods after each treatment were performed. **RESULTS:** Protective efficacy against malaria episodes was 20% (95% confidence interval [CI], 11%-29%). The frequency of malaria episodes was reduced after the first 2 sulfadoxine-pyrimethamine applications (protective efficacy, 23% [95% CI, 6%-36%] after the first dose and 17% [95% CI, 1%-30%] after the second dose). After the third treatment at month 15, however, no protection was achieved. Protection against the first or single anemia episode was only significant after the first IPTi dose (protective efficacy, 30%; 95% CI, 5%-49%). The number of anemia episodes increased after the last IPTi dose (protective efficacy, -24%; 95% CI, -50% to -2%). **CONCLUSION:** In an area of intense perennial malaria transmission, sulfadoxine-pyrimethamine-based IPTi conferred considerably lower protection than reported in areas where

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the disease is moderately or seasonally endemic. Protective efficacy is age-dependent, and extension of IPTi into the second year of life does not provide any benefit.

Malaria in pregnancy

Trop Med Int Health. 2007 Feb;12(2):209-18.

Chloroquine prophylaxis against vivax malaria in pregnancy: a randomized, double-blind, placebo-controlled trial.

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OBJECTIVE: To assess the safety of chloroquine (CQ) as prophylaxis against *Plasmodium vivax* infection during pregnancy. **METHOD:** One thousand pregnant Karen women were enrolled in a randomized, double-blind, placebo-controlled trial of chemoprophylaxis with chloroquine (500 mg phosphate (or 300 mg base) weekly). Women received a median (range) chloroquine phosphate total dose of 9500 (1500-17 500) mg. The mothers were actively followed from inclusion to delivery and their infants until 12 months of age. **RESULTS:** Chloroquine prophylaxis completely prevented *P. vivax* episodes; 10.1% (95% CI: 7.3-14.5) of women in the placebo group experienced at least one episode of vivax malaria but no episode occurred in women in the CQ group. By contrast, the numbers of *P. falciparum* episodes were similar in each group: 7.4% (95% CI: 3.7-11.1) and 5.6% (95% CI: 3.3-7.9) in the placebo and CQ groups respectively ($P = 0.56$). Chloroquine prophylaxis was well tolerated and there was no difference in the proportions of reported side effects between CQ treated and placebo groups except for the duration of palpitations and sleeping disorders which were more frequent in those who had received CQ. Chloroquine prophylaxis had no impact on maternal anaemia, birth weight, gestational age, development of newborns or on growth, neurological development or visual acuity in infants at 1 year of age. **CONCLUSION:** Chloroquine is safe and effective as prophylaxis against *P. vivax* during pregnancy in this population.

Rapid diagnostic tests

Malar J. 2007 May 16;6:58.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17506881>

Paracheck-Pf accuracy and recently treated Plasmodium falciparum infections: is there a risk of over-diagnosis?

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BACKGROUND: An assessment of the accuracy of Paracheck Pf, a malaria rapid diagnostic test (RDT) detecting histidine rich protein 2 was undertaken amongst children aged 6-59 months

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in eastern Democratic Republic of Congo. **METHODS:** This RDT assessment occurred in conjunction with an ACT efficacy trial. Febrile children were simultaneously screened with both RDT and high quality microscopy and those meeting inclusion criteria were followed for 35 days. **RESULTS:** 358 febrile children were screened with 180 children recruited for five weeks follow-up. On screening, the RDT accurately diagnosed all 235 true malaria cases, indicating 100% RDT sensitivity. Of the 123 negative slides, the RDT gave 59 false-positive results, indicating 52.0% (64/123) RDT specificity. During follow-up after treatment with an artemisinin-based combination therapy, 98.2% (110/112), 94.6% (106/112), 92.0% (103/112) and 73.5% (50/68) of effectively treated children were still false-positive by RDT at days 14, 21, 28 and 35, respectively. **CONCLUSION:** Results show that though the use of Paracheck-Pf is as sensitive as microscopy in detecting true malaria cases, a low specificity did present a high frequency of false-positive RDT results. What's more, a duration of RDT false-positivity was found that significantly surpassed the 'fortnight' after effective treatment reported by its manufacturer. Though further research is needed in assessing RDT accuracy, study results showing the presence of frequent false positivity should be taken into consideration to avoid clinicians inappropriately focusing on malaria, not identifying the true cause of illness, and providing unnecessary treatment.

BMJ. 2007 Feb 24;334(7590):403. Epub 2007 Jan 26.

<http://www.bmj.com/cgi/content/full/334/7590/403>

Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial.

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OBJECTIVE: To compare rapid diagnostic tests (RDTs) for malaria with routine microscopy in guiding treatment decisions for febrile patients. **DESIGN:** Randomised trial. **SETTING:** Outpatient departments in northeast Tanzania at varying levels of malaria transmission. **PARTICIPANTS:** 2416 patients for whom a malaria test was requested. **INTERVENTION:** Staff received training on rapid diagnostic tests; patients sent for malaria tests were randomised to rapid diagnostic test or routine microscopy **MAIN OUTCOME MEASURE:** Proportion of patients with a negative test prescribed an antimalarial drug. **RESULTS:** Of 7589 outpatient consultations, 2425 (32%) had a malaria test requested. Of 1204 patients randomised to microscopy, 1030 (86%) tested negative for malaria; 523 (51%) of these were treated with an antimalarial drug. Of 1193 patients randomised to rapid diagnostic test, 1005 (84%) tested negative; 540 (54%) of these were treated for malaria (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Children aged under 5 with negative rapid diagnostic tests were more likely to be prescribed an antimalarial drug than were those with negative slides (P=0.003). Patients with a negative test by any method were more likely to be prescribed an antibiotic (odds ratio 6.42, 4.72 to 8.75; P<0.001). More than 90% of prescriptions for antimalarial drugs in low-moderate transmission settings were for patients for whom a test requested by a clinician was negative for malaria. **CONCLUSIONS:** Although many cases of malaria are missed outside the formal sector, within it malaria is massively over-diagnosed. This threatens the sustainability of deployment of artemisinin combination treatment, and treatable bacterial diseases are likely to

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be missed. Use of rapid diagnostic tests, with basic training for clinical staff, did not in itself lead to any reduction in over-treatment for malaria. Interventions to improve clinicians' management of febrile illness are essential but will not be easy. TRIAL REGISTRATION: Clinical trials NCT00146796 [ClinicalTrials.gov].

Comment

This is a very important effectiveness trial, which shows that despite a negative RDT, most febrile children will be treated with antimalarials. In moving to more expensive artemisinin-based derivatives, and in trying to reduce resistance pressure, it was hoped that RDTs would guide treatment, reduce unnecessary prescribing and save costs. There is a lot of work to be done in understanding how to help health workers, who are used to empirical treatment based on clinical signs, to use field technology to guide treatment.

Insecticide treated materials

Trop Med Int Health. 2006 Aug;11(8):1166-77.

Insecticide-treated bednets for the prevention of Plasmodium falciparum malaria in Cambodia: a cluster-randomized trial.

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OBJECTIVES: To validate and quantify the impact of insecticide-treated bednets (ITN) on malaria morbidity and mortality in Cambodia. **METHODS:** A paired, cluster-randomized trial of ITN was conducted in Rattanakiri, North East Cambodia. Thirty-four villages with a total population of 10,726 were randomized to receive deltamethrin-impregnated bednets or to control (no net provision). Cross-sectional surveys measured Plasmodium falciparum prevalence at baseline and 10 months after ITN distribution. Village malaria volunteers in control and intervention villages treated dipstick-positive P. falciparum cases with artesunate and mefloquine. The resulting passive surveillance data were used as an estimate of the incidence of clinical P. falciparum infections. **RESULTS:** There was a protective efficacy of 28% in P. falciparum incidence (adjusted rate ratio 0.72, 95% CI 0.47-1.08) and 9% in P. falciparum prevalence (adjusted prevalence ratio 0.91, 95% CI 0.65-1.28) in ITN relative to control villages; however, neither of these estimates reached statistical significance. Individual-level analysis indicated a greater reduction in P. falciparum prevalence among under 5-year-olds (adjusted OR = 0.63, 95% CI 0.26-1.53) compared to older individuals (interaction P = 0.042). The protective efficacy of 35% (95% CI -28, 67%) with respect to clinical P. falciparum incidence in under 5-year-olds was more pronounced than the corresponding estimates for prevalence but was again not significant. **CONCLUSIONS:** Lack of statistical significance in the results is likely to be due to a lack of power. The analysis provides further evidence for ITN effectiveness in South East Asia, particularly among individuals under 5 years of age.

Treatment of uncomplicated malaria

JAMA. 2007 May 23;297(20):2210-9.

<http://jama.ama-assn.org/cgi/content/full/297/20/2210>

Combination therapy for uncomplicated falciparum malaria in Ugandan children: a randomized trial.

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CONTEXT: Combination therapy is now widely advocated as first-line treatment for uncomplicated malaria in Africa. However, it is not clear which treatment regimens are optimal or how to best assess comparative efficacies in highly endemic areas. **OBJECTIVE:** To compare the efficacy and safety of 3 leading combination therapies for the treatment of uncomplicated malaria. **DESIGN, SETTING, AND PARTICIPANTS:** Single-blind randomized clinical trial, conducted between November 2004 and June 2006, of treatment for all episodes of uncomplicated malaria in children in an urban community in Kampala, Uganda. A total of 601 healthy children (aged 1-10 years) were randomly selected and were followed up for 13 to 19 months, receiving all medical care at the study clinic. **INTERVENTIONS:** Study participants were randomized to receive 1 of 3 combination therapies (amodiaquine plus sulfadoxine-pyrimethamine, amodiaquine plus artesunate, or artemether-lumefantrine) when diagnosed with their first episode of uncomplicated malaria. The same assigned treatment was given for all subsequent episodes. **MAIN OUTCOME MEASURE:** 28-Day risk of parasitological failure (unadjusted and adjusted by genotyping to distinguish recrudescence from new infection) for each episode of uncomplicated malaria treated with study drugs. **RESULTS:** Of enrolled children, 329 of 601 were diagnosed with at least 1 episode of uncomplicated malaria, and 687 episodes of *Plasmodium falciparum* malaria were treated with study drugs. The 28-day risk of treatment failure (unadjusted by genotyping) for individual episodes of malaria were 26.1% (95% CI, 21.1%-32.1%) for amodiaquine plus sulfadoxine-pyrimethamine, 17.4% (95% CI, 13.1%-23.1%) for amodiaquine plus artesunate, and 6.7% (95% CI, 3.9%-11.2%) for artemether-lumefantrine ($P < .05$ for all pairwise comparisons). When only recrudescence treatment failures were considered, the risks of failure were 14.1% (95% CI, 10.3%-19.2%), 4.6% (95% CI, 2.5%-8.3%), and 1.0% (95% CI, 0.3%-4.0%) for the same order of study drugs, respectively ($P < \text{or} = .008$ for all pairwise comparisons, except amodiaquine plus artesunate vs artemether-lumefantrine, $P = .05$). There were no deaths or cases of severe malaria. Significant reductions in anemia (9.3% [95% CI, 7.0%-12.0%] at enrollment vs 0.6% [95% CI, 0.1%-2.2%] during the last 2 months of follow-up; $P < .001$) and asymptomatic parasitemia (18.6% [95% CI, 15.5%-22.1%] at enrollment vs 2.3% [95% CI, 1.5%-3.5%] during the last 2 months of follow-up; $P < .001$) were observed according to routine testing. **CONCLUSIONS:** Artemether-lumefantrine was the most efficacious treatment for uncomplicated malaria in the study population. With all study regimens, the provision of prompt and reasonably effective facility-based treatment was associated with good outcomes in long-term health measures. **TRIAL REGISTRATION:** isrctn.org Identifier: ISRCTN37517549.

JAMA. 2007 May 23;297(20):2201-9.

<http://jama.ama-assn.org/cgi/content/full/297/20/2201>

Sulfadoxine-pyrimethamine, chlorproguanil-dapsone, or chloroquine for the treatment of Plasmodium vivax malaria in Afghanistan and Pakistan: a randomized controlled trial.

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CONTEXT: In areas where Plasmodium falciparum and Plasmodium vivax coexist and treatments for the 2 species differ, misdiagnosis can lead to poor outcomes in either disease. A unified therapy effective against both species would reduce reliance on species-specific diagnosis, which in many areas is difficult to maintain. The antifolates are an important and affordable antimalarial class to which it is often assumed P vivax malaria is intrinsically resistant. **OBJECTIVE:** To test the relative efficacy and safety of 2 antifolate drugs against P vivax malaria and compare each with chloroquine. **DESIGN, SETTING, AND PATIENTS:** An open-label randomized controlled trial comparing chloroquine, sulfadoxine-pyrimethamine, and chlorproguanil-dapsone for the treatment of P vivax malaria was conducted in eastern Afghanistan and northwestern Pakistan, areas in which P vivax malaria predominates. A total of 20,410 patients older than 3 years were screened; 767 patients (315 in Pakistan and 452 in Afghanistan) with confirmed P vivax malaria were enrolled and followed up daily for 4 days, then weekly for 28 days, between March 2004 and June 2006. **MAIN OUTCOME MEASURES:** Complete clearance of parasites with no recrudescence by day 14. Secondary outcomes included being parasite-free by day 28, clinical failure, and anemia. **RESULTS:** By day 14, only 1 patient in the sulfadoxine-pyrimethamine group had parasites. By day 28, failure rates were found in 2 of 153 patients (1.3%) in the chloroquine group, 5 of 290 patients (1.7%) in the sulfadoxine-pyrimethamine group, and 27 of 272 patients (9.9%) in the chlorproguanil-dapsone group. Chlorproguanil-dapsone was less effective than sulfadoxine-pyrimethamine (adjusted odds ratio [OR], 6.4; 95% confidence interval [CI], 2.4-17.0; P<.001) and chloroquine (adjusted OR, 8.4; 95% CI, 2.0-36.5; P = .004). Chloroquine and sulfadoxine-pyrimethamine were equivalent in efficacy at day 28 (adjusted OR, 1.3; 95% CI, 0.3-7.0; P = .73). Chloroquine cleared gametocytes and asexual parasites more rapidly than sulfadoxine-pyrimethamine or chlorproguanil-dapsone did. All drugs were well tolerated. **CONCLUSIONS:** Although chloroquine remains the drug of choice, antifolates are effective against P vivax malaria in South Asia. These drugs may be appropriate for unified treatment where species-specific diagnosis is unavailable, most likely in combination with other drugs. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00158561.

Lancet. 2007 Mar 3;369(9563):757-65.

Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison.

Ratcliff A, Siswantoro H, Kenangalem E, Maristela R, Wuwung RM, Laihad F, Ebsworth

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EP, Anstey NM, Tjitra E, Price RN.

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BACKGROUND: The burden of *Plasmodium vivax* infections has been underappreciated, especially in southeast Asia where chloroquine resistant strains have emerged. Our aim was to compare the safety and efficacy of dihydroartemisinin-piperaquine with that of artemether-lumefantrine in patients with uncomplicated malaria caused by multidrug-resistant *P falciparum* and *P vivax*. **METHODS:** 774 patients in southern Papua, Indonesia, with slide-confirmed malaria were randomly assigned to receive either artemether-lumefantrine or dihydroartemisinin-piperaquine and followed up for at least 42 days. The primary endpoint was the overall cumulative risk of parasitological failure at day 42 with a modified intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, trial number 00157833. **FINDINGS:** Of the 754 evaluable patients enrolled, 466 had infections with *P falciparum*, 175 with *P vivax*, and 113 with a mixture of both species. The overall risk of failure at day 42 was 43% (95% CI 38-48) for artemether-lumefantrine and 19% (14-23) for dihydroartemisinin-piperaquine (hazard ratio=3.0, 95% CI 2.2-4.1, $p<0.0001$). After correcting for reinfections, the risk of recrudescence of *P falciparum* was 4.4% (2.6-6.2) with no difference between regimens. Recurrence of *vivax* occurred in 38% (33-44) of patients given artemether-lumefantrine compared with 10% (6.9-14.0) given dihydroartemisinin-piperaquine ($p<0.0001$). At the end of the study, patients receiving dihydroartemisinin-piperaquine were 2.0 times (1.2-3.6) less likely to be anaemic and 6.6 times (2.8-16) less likely to carry *vivax* gametocytes than were those given artemether-lumefantrine. **INTERPRETATION:** Both dihydroartemisinin-piperaquine and artemether-lumefantrine were safe and effective for the treatment of multidrug-resistant uncomplicated malaria. However, dihydroartemisinin-piperaquine provided greater post-treatment prophylaxis than did artemether-lumefantrine, reducing *P falciparum* reinfections and *P vivax* recurrences, the clinical public-health importance of which should not be ignored.

Am J Trop Med Hyg. 2007 Apr;76(4):614-8.

Unusual pattern of *Plasmodium falciparum* drug resistance in the northwestern Peruvian Amazon region.

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High levels of *Plasmodium falciparum* resistance to both chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) have been documented throughout the Amazon Basin of South America. Because of reports about the persistent efficacy of both of these drugs in the northwestern Peruvian Amazon region, we carried out an evaluation of the therapeutic efficacy of chloroquine (25 mg/kg) and SP (25 mg/kg of the sulfadoxine component) for the treatment of uncomplicated *P. falciparum* infections at two sites: Ullpayacu and Pampa Hermoza/Alianza. A total of 111 patients were enrolled. Only 5 (14.3%) of the 35 patients who received CQ had an adequate clinical and parasitologic response (ACPR). Six subjects (17%) had early treatment failure, 1 (2.9%) had late clinical failure, and 23 (65.7%) had late parasitologic failure (LPF). Of the subjects treated with SP, 92.3% had ACPR and 7.7% had LPF. Based on these findings, it is

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clear that there are at least limited areas within the Peruvian Amazon region where *P. falciparum* strains continue to be sensitive to SP.

Malar J. 2007 Feb 28;6:25.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17328806>

Artemisinin-based combination therapy for uncomplicated Plasmodium falciparum malaria in Colombia.

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BACKGROUND: Artemisinin-based combination therapy (ACT) is being widely promoted as a strategy to counteract the increase in *Plasmodium falciparum* antimalarial drug resistance. **METHODS:** A randomized, double-blind, placebo-controlled, clinical trial of the efficacy, effect on gametocytes and safety of the addition of artesunate/placebo (4 mg/kg/day x 3 d) to amodiaquine (10 mg/kg/day x 3 d) was conducted in Choco department, a low intensity transmission area in northwest Colombia. **RESULTS:** From 2,137 screened subjects, 85 entered the study: 43 in the amodiaquine plus placebo and 42 in the amodiaquine plus artesunate groups. Potentially eligible cases failed to qualify mostly because they were not available for follow-up visits (73%). Based on a per protocol analysis, the therapeutic response to both treatments was high: amodiaquine/placebo 35/36, 97.2% (95% CI 85.5-99.9), and amodiaquine/artesunate 32/32, 100% (89.1-100) after PCR genotyping. The Kaplan-Meier survival estimates based on all eligible patients enrolled (amodiaquine/placebo: n = 42; amodiaquine/artesunate: n = 41) were similar in the two study groups (P = 0.3). The addition of artesunate significantly decreased gametocyte carriage on Day 4 (OR = 0.1 95% CI 0.02-0.6), Day 7 (OR = 0.2 95% CI 0.04-0.9), Day 14 (OR = 0.09 95% CI 0-0.8), and Day 21 (OR 95% CI 0-0.9). Most subjects in both groups (81% in amodiaquine/placebo and 75.6% in amodiaquine/artesunate) reported at least one drug related adverse event. Symptoms were generally mild and self-limiting and there was no serious adverse event. Two patients on amodiaquine/artesunate voluntarily withdrew from study because they could not tolerate the medication. **CONCLUSION:** Both drug regimens were effective in this area of Colombia. The addition of artesunate reduced gametocyte carriage and did not adversely affect tolerability. In this set of patients, the rate of adverse events was higher than in other studies. Patients' follow-up is problematic in areas with dispersed population and affects the conduct of clinical studies and monitoring of treatment effects. The results are discussed in the light of concurrent increase resistance to amodiaquine in other endemic areas in Colombia and the factors that may influence a change in the national antimalarial drug policy.

Trop Med Int Health. 2007 Feb;12(2):251-9.

A randomized open study to assess the efficacy and tolerability of dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Cambodia.

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OBJECTIVES: To compare the efficacy and tolerability of dihydroartemisinin-piperaquine (DHA-PQP) with that of a 3-day regimen of mefloquine and artesunate (MAS3) for the treatment of uncomplicated falciparum malaria in Cambodia. **METHOD:** Randomized open-label non-inferiority study over 64 days. **RESULTS:** Four hundred and sixty-four patients were included in the study. The polymerase chain reaction genotyping-adjusted cure rates on day 63 were 97.5% (95% confidence interval, CI, 93.8-99.3) for DHA-PQP and 97.5% (95% CI, 93.8-99.3) for MAS3, $P = 1$. There were no serious adverse events, but significantly more episodes of vomiting ($P = 0.03$), dizziness ($P = 0.002$), palpitations ($P = 0.04$), and sleep disorders ($P = 0.03$) reported in the MAS3 treatment group, consistent with the side-effect profile of mefloquine. **CONCLUSIONS:** DHA-PQP was as efficacious as MAS3, but much better tolerated, making it more appropriate for use in a routine programme setting. This highly efficacious, safe and more affordable fixed-dose combination could become the treatment of choice for Plasmodium falciparum malaria in Cambodia.

Lancet. 2007 Feb 10;369(9560):491-8.

Artemether-lumefantrine versus amodiaquine plus sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Burkina Faso: a randomised non-inferiority trial.

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BACKGROUND: Artemisinin-based combination regimens are widely advocated for malarial treatment, but other effective regimens might be cheaper and more readily available. Our aim was to compare the risk of recurrent parasitaemia in patients given artemether-lumefantrine with that in those given amodiaquine plus sulfadoxine-pyrimethamine for uncomplicated malaria. **METHODS:** We enrolled 521 patients aged 6 months or older with uncomplicated falciparum malaria in Bobo-Dioulasso, Burkina Faso. Patients were randomly assigned to receive standard doses of either artemether-lumefantrine (261) or amodiaquine plus sulfadoxine-pyrimethamine (260) for 3 days. Primary endpoints were the risks of treatment failure within 28 days, either unadjusted or adjusted by genotyping to distinguish recrudescence from new infection. The study is registered at controlled-trials.gov with the identifier ISRCTN54261005. **FINDINGS:** Of enrolled patients, 478 (92%) completed the 28-day study. The risk of recurrent symptomatic malaria was lowest in the group given amodiaquine plus sulfadoxine-pyrimethamine (1.7% vs 10.2%; risk difference 8.5%; 95% CI 4.3-12.6; $p=0.0001$); as was the risk of recurrent parasitaemia (4.7% vs 15.1%; 10.4%; 5.1-15.6; $p=0.0002$). Nearly all recurrences were due to new infections. Recrudescences were four late treatment failures with artemether-lumefantrine and one early treatment failure with amodiaquine plus sulfadoxine-pyrimethamine. Both regimens were safe and well tolerated, with pruritus more common with amodiaquine plus sulfadoxine-pyrimethamine than with artemether-lumefantrine. Each regimen selected for new

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isolates with mutations that have been associated with decreased drug susceptibility.
INTERPRETATION: Amodiaquine plus sulfadoxine-pyrimethamine was more effective than was artemether-lumefantrine for the treatment of uncomplicated malaria. For regions of Africa where amodiaquine plus sulfadoxine-pyrimethamine continues to be effective, this less expensive and more available regimen should be considered as an alternative to blanket recommendations for artemisinin-based combination treatment for malaria.

Antimicrob Agents Chemother. 2007 Mar;51(3):991-7. Epub 2006 Dec 28.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17194834>

Amodiaquine and artemether-lumefantrine select distinct alleles of the Plasmodium falciparum mdr1 gene in Tanzanian children treated for uncomplicated malaria.

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The artemisinin-based combination therapies artemether-lumefantrine (AL) and amodiaquine (AQ) plus artesunate have been adopted for treatment of Plasmodium falciparum malaria in many African countries. Molecular markers of parasite resistance suitable for surveillance have not been established for any of the component drugs in either of these combinations. We assessed P. falciparum mdr1 (Pfmdr1) alleles present in 300 Tanzanian children presenting with uncomplicated falciparum malaria, who were enrolled in a clinical trial of antimalarial therapy. Pfmdr1 genotype analysis was also performed with isolates from 182 children who failed AQ monotherapy and 54 children who failed AL treatment. Pfmdr1 alleles 86Y, 184Y, and 1246Y were more common among treatment failures in the AQ group than among pretreatment infections. The converse was found in the AL-treated group. Children presenting with the 86Y/184Y/1246Y Pfmdr1 haplotype and treated with AQ were significantly more likely to retain this haplotype if they were parasite positive during posttreatment follow-up than were children treated with AL (odds ratio, 33.25; 95% confidence interval, 4.17 to 1441; P, <0.001). We conclude that AL and AQ exert opposite within-host selective effects on the Pfmdr1 gene of P. falciparum.

Malar J. 2006 Nov 24;5:113.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17125496>

Efficacy of three artemisinin combination therapies for the treatment of uncomplicated Plasmodium falciparum malaria in the Republic of Congo.

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BACKGROUND: Presented here are the results of a comparative trial on the efficacy of three artemisinin-based combinations conducted from May to October 2004, in Pool Province, Republic of Congo. **METHODS:** The main outcome was the proportion of cases of true treatment success at day 28. Recrudescences were distinguished from re-infections by PCR analysis. A total of 298 children of 6-59 months were randomized to receive either artesunate + SP (AS+SP), artesunate + amodiaquine (AS+AQ) or artemether + lumefantrine (AL), of which 15 (5%) were lost to follow-up. **RESULTS:** After 28 days, there were 21/85 (25%) recurrent parasitaemias in the AS+SP group, 31/97 (32%) in the AS+AQ group and 13/100 (13%) in the AL group. The 28-day PCR-corrected cure rate was 90.1% [95% CI 80.7-95.9] for AS+SP, 98.5% [95% CI 92.0-100] for AS+AQ and 100% [95.8-100] for AL, thereby revealing a weaker response to AS+SP than to AL ($p = 0.003$) and to AS+AQ ($p = 0.06$). A potential bias was the fact that children treated with AL were slightly older and in better clinical condition, but logistic regression did not identify these as relevant factors. There was no significant difference between groups in fever and parasite clearance time, improvement of anaemia and gametocyte carriage at day 28. No serious adverse events were reported. **CONCLUSION:** Considering the higher efficacy of AL as compared to AS+SP and the relatively high proportion of cases with re-infections in the AS+AQ group, we conclude that AL is clinically more effective than AS+SP and AS+AQ in this area of the Republic of Congo. Implementation of the recently chosen new national first-line AS+AQ should be monitored closely.

Acta Trop. 2006 Nov;100(1-2):142-50. Epub 2006 Nov 20.

Improved efficacy with amodiaquine instead of chloroquine in sulfadoxine/pyrimethamine combination treatment of falciparum malaria in Uganda: experience with fixed-dose formulation.

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Amodiaquine (AQ) is an affordable compound, chemically related to chloroquine (CQ) but often effective against CQ resistant *Plasmodium falciparum*. In Uganda, a pre-packed fixed-dose combination of CQ plus sulfadoxine/pyrimethamine (CQ+SP) called Homapak is used in the home based management of fever program (HBM). We performed a single blind randomized trial to determine the efficacy of AQ+SP in comparison with the fixed-dose CQ+SP (Homapak) in the treatment of uncomplicated falciparum malaria in Ugandan children aged 6 months to 5 years. The study was done in 2004 at Walkuba Health Center, a sub-urban area in Jinja district, Uganda. Primary outcome was the day 14 per protocol clinical and parasitological response according to the WHO. A total of 183 children were included (mean age 28 months) and 90% completed 28 days of follow up. The day 14 adequate clinical and parasitological response was

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70.9% for CQ+SP and 97.4% for AQ+SP ($p<0.001$). In those given CQ+SP, treatment failure rates for the 6 months to 2 years age group were much higher (48.2%) than in the older children (18.2%, $p=0.004$). The day 28 PCR adjusted parasitological failure rates were also higher in the CQ+SP (31.3%) than in the AQ+SP group (13.1%) ($p=0.003$), with a higher gametocyte carriage among the CQ+SP group. We conclude that the efficacy of AQ+SP was significantly superior to the fixed-dose CQ+SP (Homapak), particularly among the youngest children. Thus, AQ could be used instead of CQ in combination with SP to improve the effectiveness against falciparum malaria in Uganda.

Trop Med Int Health. 2006 Nov;11(11):1653-60.

An open label randomized comparison of mefloquine-artesunate as separate tablets vs. a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand.

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BACKGROUND: Delivering drugs in a fixed combination is essential to the success of the strategy of artemisinin-based combination therapy. This prevents one drug being taken without the protection of the other, reducing the chance of emergence and spread of drug resistant strains of *Plasmodium falciparum*. A lower tablet burden should also facilitate adherence to treatment. A new fixed combination of mefloquine plus artesunate has been developed. This was compared with the conventional regimen of separate tablets for the treatment of uncomplicated multidrug-resistant falciparum malaria. **METHODS:** On the north-western border of Thailand 500 adults and children with uncomplicated falciparum malaria were randomized to receive either the new fixed combination or separate tablets. They were followed up weekly for 63 days. **RESULTS:** The day 63 polymerase chain reaction-adjusted cure rates were 91.9% (95% CI 88.2-95.6) in the fixed combination group and 89.2% (85.0-93.4) in the loose tablets group ($P=0.3$). There was a lower incidence of early vomiting in the group receiving the fixed combination. **CONCLUSION:** This new fixed combination of mefloquine and artesunate was efficacious, well tolerated and convenient to administer.

Am J Trop Med Hyg. 2006 Oct;75(4):630-6.

A randomized trial of artesunate-sulfamethoxypyrazine-pyrimethamine versus artemether-lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Mali.

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The choice of artemisinin-based combination that is being adopted for malaria treatment in sub-Saharan Africa may depend on several factors, including cost, efficacy, side effects, and simplicity of administration. We tested the hypothesis that artesunate-sulfamethoxypyrazine-pyrimethamine is as efficacious as the four-dose regimen of artemether-lumefantrine for treatment of *Plasmodium falciparum* malaria. The study was carried out during two transmission seasons (2003 and 2004) in Sotuba, Mali. Participants at least 6 months of age with uncomplicated *P. falciparum* malaria were randomly assigned to receive artesunate-sulfamethoxypyrazine-pyrimethamine or artemether-lumefantrine. Treatment efficacy was assessed using the World Health Organization 28-day protocol. A total of 606 (303 in each arm) patients were enrolled. The cure rate was higher for artesunate-sulfamethoxypyrazine-pyrimethamine than for artemether-lumefantrine (98.7% versus 89.6%; $P < 0.0001$). After correction for cases of re-infection, the cure rates were 100% and 99.0%, respectively ($P = 0.08$). No serious adverse events occurred. Artesunate-sulfamethoxypyrazine-pyrimethamine is well-tolerated and effective against *P. falciparum* malaria. It showed an additional benefit of preventing new infections.

Trop Med Int Health. 2006 Oct;11(10):1503-11.

Artesunate + amodiaquine and artesunate + sulphadoxine-pyrimethamine for treatment of uncomplicated malaria in Democratic Republic of Congo: a clinical trial with determination of sulphadoxine and pyrimethamine-resistant haplotypes.

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We undertook a trial of artesunate + amodiaquine (AS + AQ) and artesunate + sulphadoxine-pyrimethamine (AS + SP) in 180 children of age 6-59 months with uncomplicated malaria in Democratic Republic of Congo. Children were randomly allocated to receive 3 days observed treatment of AS + AQ ($n = 90$) or 3 days of AS + SP ($n = 90$). Primary efficacy outcomes were 28-day parasite recurrence rates, and recrudescence rates were adjusted by genotyping to distinguish new infection and recrudescence. In addition, we determined the prevalence of molecular markers of resistance to sulphadoxine and pyrimethamine. Day 28 parasite recurrence rates were 16.9% (14/83; 95% CI: 9.5-26.7) in the AS + AQ group and 34.6% (28/81; 95% CI: 24.3-46.0) in the AS + SP group ($P = 0.009$). After PCR correction, recrudescence rates were 6.7% (5/74; 95% CI: 2.2-15.1) for AS + AQ and 19.7% (13/66; 95% CI: 10.9-31.3) for AS + SP ($P = 0.02$). There was no significant difference between the two arms in time to parasite clearance, fever clearance and gametocyte clearance. Parasite genotyping showed high frequencies of dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) molecular SP-resistance markers, with 57% of the samples showing more than three mutations linked to SP resistance, and 27% with triple-dhfr/double-dhps haplotype, confirming that SP treatment failure rates are likely to be high. AS + AQ had significantly higher efficacy than AS + SP. These results contributed to the subsequent change to AS + AQ as first-line regimen in the country. Efforts to properly implement the new protocol and maintain adherence at acceptable levels should include health staff and patient sensitization. The 6.8% recrudescence rate indicates that AS + AQ should be monitored closely until a more effective artemisinin combination therapy regimen is needed and can be introduced.

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Trop Med Int Health. 2006 Aug;11(8):1157-65.

An open, randomized comparison of artesunate plus mefloquine vs. dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in the Lao People's Democratic Republic (Laos).

Mayxay M, Thongpraseuth V, Khanthavong M, Lindegårdh N, Barends M, Keola S, Pongvongsa T, Phompida S, Phetsouvanh R, Stepniewska K, White NJ, Newton PN.

Wellcome Trust, Mahosot Hospital, Oxford Tropical Medicine Research Collaboration, Mahosot Hospital, Vientiane, Lao PDR.

OBJECTIVE: To determine the efficacy and safety of oral dihydroartemisinin-piperaquine (DP, Artekin) in the treatment of uncomplicated Plasmodium falciparum malaria in southern Laos. **METHODS:** An open, randomized clinical trial of oral artesunate-mefloquine (AM) vs. DP in 220 patients with acute uncomplicated falciparum malaria in Savannakhet Province, Laos. **RESULTS:** The 42-day cure rates (95% CI), as determined by survival analysis and adjusted for reinfection, were excellent and similar for the two groups [99 (94-100)% and 100 (100-100)% for AM and DP, respectively]. The median (range) fever and parasite clearance times for the AM and DP groups were also similar [20 (4-63) h and 2 (1-4) days vs. 20 (7-57) and 2 (1-4) days, logrank $P = 0.4$ and 0.17 , respectively]. There were more patients with at least one potential side effect following treatment in the AM group when compared with the DP group [64/110 (58%) vs. 48/110 (44%), respectively, $P = 0.031$]. **CONCLUSION:** Dihydroartemisinin-piperaquine did not have superior efficacy to AM for the treatment of uncomplicated falciparum malaria in Laos but was associated with fewer adverse effects.

PLoS Clin Trials. 2006 May;1(1):e7. Epub 2006 May 19.
<http://clinicaltrials.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pctr.0010007>

Artemisinin combination therapies for treatment of uncomplicated malaria in Uganda.

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OBJECTIVES: To compare the efficacy and safety of artemisinin combination therapies for the treatment of uncomplicated falciparum malaria in Uganda. **DESIGN:** Randomized single-blind controlled trial. **SETTING:** Tororo, Uganda, an area of high-level malaria transmission. **PARTICIPANTS:** Children aged one to ten years with confirmed uncomplicated P. falciparum malaria. **INTERVENTIONS:** Amodiaquine + artesunate or artemether-lumefantrine.

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OUTCOME MEASURES: Risks of recurrent symptomatic malaria and recurrent parasitemia at 28 days, unadjusted and adjusted by genotyping to distinguish recrudescences and new infections. **RESULTS:** Of 408 participants enrolled, 403 with unadjusted efficacy outcomes were included in the per-protocol analysis. Both treatment regimens were highly efficacious; no recrudescences occurred in patients treated with amodiaquine + artesunate, and only two occurred in those treated with artemether-lumefantrine. However, recurrent malaria due to new infections was common. The unadjusted risk of recurrent symptomatic malaria was significantly lower for participants treated with artemether-lumefantrine than for those treated with amodiaquine + artesunate (27% versus 42%, risk difference 15%, 95% CI 5.9%-24.2%). Similar results were seen for the risk of recurrent parasitemia (51% artemether-lumefantrine versus 66% amodiaquine + artesunate, risk difference 16%, 95% CI 6.2%-25.2%). Amodiaquine + artesunate and artemether-lumefantrine were both well-tolerated. Serious adverse events were uncommon with both regimens. **CONCLUSIONS:** Amodiaquine + artesunate and artemether-lumefantrine were both highly efficacious for treatment of uncomplicated malaria. However, in this holoendemic area, despite the excellent performance of both regimens in terms of efficacy, many patients experienced recurrent parasitemia due to new infections. Artemether-lumefantrine was superior to amodiaquine + artesunate for prevention of new infections. To maximize the benefit of artemisinin combination therapy in Africa, treatment should be integrated with strategies to prevent malaria transmission. The impact of frequent repeated therapy on the efficacy, safety, and cost-effectiveness of new artemisinin regimens should be further investigated.

Am J Trop Med Hyg. 2006 Jul;75(1):143-5.

<http://www.ajtmh.org/cgi/content/full/75/1/143>

High efficacy of two artemisinin-based combinations (artesunate + amodiaquine and artemether + lumefantrine) in Caala, Central Angola.

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In April 2004, 137 children 6-59 months of age with uncomplicated *Plasmodium falciparum* (Pf) malaria (Caala, Central Angola) were randomized to receive either artemether-lumefantrine (Coartem) or artesunate + amodiaquine (ASAQ). After 28 days of follow-up, there were 2/61 (3.2%) recurrent parasitemias in the Coartem group and 4/64 (6.2%) in the ASAQ group ($P = 0.72$), all classified as re-infections after PCR genotyping (cure rate = 100% [95%CI: 94-100] in both groups). Only one patient (ASAQ group) had gametocytes on day 28 versus five (Coartem) and three (ASAQ) at baseline. Compared with baseline, anemia was significantly improved after 28 days of follow-up in both groups (Coartem: from 54.1% to 13.4%; ASAQ: from 53.1% to 15.9%). Our findings are in favor of a high efficacy of both combinations in Caala. Now that Coartem has been chosen as the new first-line anti-malarial, the challenge is to insure that this drug is available and adequately used.

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Trans R Soc Trop Med Hyg. 2006 Dec;100(12):1105-11. Epub 2006 Jun 12.

Safety and efficacy of dihydroartemisinin/piperaquine (Artekin) for the treatment of uncomplicated Plasmodium falciparum malaria in Rwandan children.

Karema C, Fanello CI, van Overmeir C, van Geertruyden JP, van Doren W, Ngamije D, D'Alessandro U.

National Malaria Control Program, Kigali, Rwanda.

In Rwanda, amodiaquine+sulfadoxine/pyrimethamine (AQ+SP) is the current first-line treatment for malaria, introduced in 2001 as an interim strategy before the future deployment of an artemisinin-based combination treatment (ACT). Dihydroartemisinin/piperaquine (DHA-PQP) is a new co-formulated and well tolerated ACT increasingly used in Southeast Asia where it has proved to be highly effective against Plasmodium falciparum malaria. We tested the efficacy, safety and tolerability of DHA-PQP in children with uncomplicated P. falciparum malaria. A randomised, open trial was carried out in 2003-2004. Seven hundred and sixty-two children aged 12-59 months with uncomplicated P. falciparum malaria were randomly allocated to one of the following treatments: amodiaquine+artesunate; AQ+SP; or DHA-PQP. Patients were followed-up until Day 28 after treatment. Adverse events and clinical and parasitological outcomes were recorded. Children treated with DHA-PQP or AQ+AS had a significantly higher cure rate compared with those treated with amodiaquine+sulfadoxine/pyrimethamine (95.2% and 92.0% vs. 84.7%, respectively). Parasite clearance was significantly faster in children treated with DHA-PQP and AQ+AS compared with those treated with amodiaquine+sulfadoxine/pyrimethamine. The frequency of adverse events was significantly lower in patients treated with DHA-PQP than in those treated with combinations containing amodiaquine. A 3-day treatment with DHA-PQP proved to be efficacious with a good safety and tolerability profile and could be a good candidate for the next first-line treatment.

N Engl J Med. 2006 Nov 9;355(19):1959-66.

Return of chloroquine antimalarial efficacy in Malawi.

Laufer MK, Thesing PC, Eddington ND, Masonga R, Dzinjalama FK, Takala SL, Taylor TE, Plowe CV.

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BACKGROUND: In 1993, Malawi became the first country in Africa to replace chloroquine with the combination of sulfadoxine and pyrimethamine for the treatment of malaria. At that time, the clinical efficacy of chloroquine was less than 50%. The molecular marker of chloroquine-resistant falciparum malaria subsequently declined in prevalence and was undetectable by 2001, suggesting that chloroquine might once again be effective in Malawi. **METHODS:** We conducted a randomized clinical trial involving 210 children with uncomplicated Plasmodium falciparum malaria in Blantyre, Malawi. The children were treated with either chloroquine or sulfadoxine/pyrimethamine and followed for 28 days to assess

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the antimalarial efficacy of the drug. RESULTS: In analyses conducted according to the study protocol, treatment failure occurred in 1 of 80 participants assigned to chloroquine, as compared with 71 of 87 participants assigned to sulfadoxine\#8211;pyrimethamine. The cumulative efficacy of chloroquine was 99% (95% confidence interval [CI], 93 to 100), and the efficacy of sulfadoxine\#8211;pyrimethamine was 21% (95% CI, 13 to 30). Among children treated with chloroquine, the mean time to parasite clearance was 2.6 days (95% CI, 2.5 to 2.8) and the mean time to the resolution of fever was 10.3 hours (95% CI, 8.1 to 12.6). No unexpected adverse events related to the study drugs occurred. CONCLUSIONS: Chloroquine is again an efficacious treatment for malaria, 12 years after it was withdrawn from use in Malawi. (ClinicalTrials.gov number, NCT00125489 [ClinicalTrials.gov].). Copyright 2006 Massachusetts Medical Society.

Comment

This is good news, as is the study from Burkina Faso (Lancet. 2007;369:491-8 suggesting that amodiaquine and SP is just as effective as the newer and more expensive artemether-lumefantrine combination in that country. While most countries are having to change to artemisinin-based combination therapies for complicated or severe malaria, what to do about uncomplated malaria is a major issue of cost effectiveness. Some countries are using Coartem (artemether lumefantrine) as first-line therapy, however it is encouraging that in some settings older regimens remain (or are again) effective.

Treatment of severe or complicated malaria

Trop Med Int Health. 2006 Nov;11(11):1643-52.

A randomised, double-blind, placebo-controlled trial of atovaquone-proguanil vs. sulphadoxine-pyrimethamine in the treatment of malarial anaemia in Zambian children.

Mulenga M, Malunga F, Bennett S, Thuma PE, Shulman C, Fielding K, Allouche A, Greenwood BM.

Tropical Diseases Research Centre, Ndola, Zambia.

OBJECTIVE: To compare the efficacy of atovaquone-proguanil (AP) and sulphadoxine-pyrimethamine (SP) in the treatment of malarial anaemia in Zambian children. METHODS: An individually randomised, double-blind, controlled trial was undertaken in Zambian children with moderately severe anaemia and Plasmodium falciparum parasitaemia. The main trial endpoint was treatment failure defined as a need for blood transfusion or treatment with quinine, persistent anaemia or death within 14 days from the start of treatment. Secondary endpoints were parasitological and haematological findings 14 or 28 days after the start of treatment. RESULTS: A total of 128 children with a packed cell volume of <21% and >9% and P. falciparum parasitaemia received treatment with AP and 127 treatment with SP. Treatment failure occurred in 28 children (22%) who received SP and in 10 (8%) who received AP (OR: 3.34, 95% CI: 1.54, 7.21). Ten children required blood transfusion, all of whom were in the SP

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treatment group. Six children died, five of whom were in the AP group; none of the deaths were considered to be related directly to treatment. CONCLUSIONS: Atovaquone-proguanil proved more effective than SP in the treatment of malarial anaemia in an area with a modest level of SP resistance. AP is no longer available through the Malarone Donation Programme and is too expensive for routine use in Africa. However, this study has shown that in an area with a modest level of resistance to SP, use of a more effective antimalaria reduces the need for blood transfusion in children with malarial anaemia.

Expert Rev Anti Infect Ther. 2007 Apr;5(2):199-204.

Artesunate, artemether or quinine in severe Plasmodium falciparum malaria?

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Quinine and the artemisinin-derivative drugs artesunate and artemether are effective treatments for severe falciparum malaria. Trials comparing artemether with quinine have not demonstrated convincing evidence of a mortality advantage for artemether. The South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT), a multicenter, randomized, open-label trial in 1461 adults with severe malaria in Asia compared artesunate with quinine. Mortality was 15% in the artesunate group and 22% in the quinine group, a reduction of 34.7% (95% confidence interval: 18.5-47.6%) in the artesunate group, with almost all the benefit reported in those with high parasite counts. Artesunate should constitute first-line treatment for severe malaria in Asia. These results can probably be generalized to the treatment of severe malaria in adults from all areas, especially in those with hyperparasitemia. However, it is unclear whether these results can be generalized to children in Africa, who constitute the majority of those who die from severe malaria worldwide.

Am J Trop Med Hyg. 2007 Jan;76(1):1-6.

Dihydroartemisinin suppository in moderately severe malaria: comparative efficacy of dihydroartemisinin suppository versus intramuscular artemether followed by oral sulfadoxine-pyrimethamine in the management of moderately severe malaria in Nigerian children.

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We compared two dose forms of artemisinin derivatives, dihydroartemisinin suppository (DHA) and intramuscular artemether (ART), in children 6 months to 10 years of age with moderately severe malaria for which oral therapy was not appropriate. Children were randomly allocated to receive three daily doses of DHA or ART followed by a single oral dose of sulfadoxine-

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pyrimethamine on the third day of both treatment regimens and were monitored for parasitologic and clinical response for 14 days. At enrollment, parasite density was 1,640-523,333/microL (geometric mean parasite density [GMPD] = 58,129/microL) in patients treated with DHA, whereas that for children who received ART was 1,440-559,400/microL (GMPD = 60,387/microL). Mean parasite and fever clearance times were similar in both groups. Days 14 and 28 parasitologic cure rates were 100% (34 of 34) and 96.2% (25 of 26) versus 96.2% (25 of 26) and 91.7% (22 of 24) for children treated with DHA and ART, respectively. In conclusion, both treatment regimens were efficacious and well tolerated.

Malar J. 2006 Jul 19;5:59.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16854236>

Supervised versus unsupervised antimalarial treatment with six-dose artemether-lumefantrine: pharmacokinetic and dosage-related findings from a clinical trial in Uganda.

Checchi F, Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, Ruzagira E, Babigumira J, Kigozi I, Kiguli J, Kyomuhendo J, Ferradini L, Taylor WR, Guthmann JP.

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BACKGROUND: A six-dose antimalarial regimen of artemether-lumefantrine (A/L) may soon become one of the most widely used drug combination in Africa, despite possible constraints with adherence and poor absorption due to inadequate nutrition, and a lack of pharmacokinetic and effectiveness data. **METHODS:** Within a trial of supervised versus unsupervised A/L treatment in a stable Ugandan Plasmodium falciparum transmission setting, plasma lumefantrine concentrations were measured in a subset of patients on day 3 (C [lum]day3) and day 7 (C [lum]day7) post-inclusion. Predictors of lumefantrine concentrations were analysed to show how both C [lum]day7 and the weight-adjusted lumefantrine dose affect 28-day recrudescence and re-infection risks. The implications of these novel findings are discussed in terms of the emergence of lumefantrine-resistant strains in Africa. **RESULTS:** C [lum]day3 and C [lum]day7 distributions among 241 supervised and 238 unsupervised patients were positively skewed. Unsupervised treatment and decreasing weight-adjusted lumefantrine dose were negatively associated with C [lum]day3. Unsupervised treatment and decreasing age showed strong negative associations with C [lum]day7. Both models were poorly predictive (R-squared < 0.25). There were no recrudescences in either arm, but decreasing lumefantrine dose per Kg resulted in up to 13-fold higher adjusted risks of re-infection. Re-infections occurred only among patients with C [lum]day7 below 400 ng/mL (p < 0.001). **CONCLUSION:** Maintaining the present six-dose regimen and ensuring high adherence and intake are essential to maximize the public health benefits of this valuable drug combination.

Malnutrition

(see also Supportive Care)

J Pediatr Gastroenterol Nutr. 2007 Mar;44(3):365-74.

Wasting and intestinal barrier function in children taking alanyl-glutamine-supplemented enteral formula.

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OBJECTIVE: We examined the effect of a diet supplemented with alanyl-glutamine (AG) or placebo glycine (G) on intestinal barrier function and growth in children in northeastern Brazil. **PATIENTS AND METHODS:** One hundred seven children ages 7.9 to 82.2 months with a weight-for-age (WAZ), height-for-age (HAZ), or weight-for-height (WHZ) z-score less than -1 were studied. From July 2003 to November 2004, 51 study patients received AG (24 g/d) and 56 received G (25 g/d; isonitrogenic concentration) control for 10 days. Lactulose/mannitol excretion ratio was used as a measure of intestinal permeability and was performed on days 1 and 10 of nutritional supplementation. Weight and height were measured on days 1, 10, 30, and 120 of the protocol. **RESULTS:** The patients were similar on admission with regard to age, sex, birth weight, nutritional status, lactulose/mannitol ratio, and serum concentrations of glutamine and arginine. The percentage of lactulose urinary excretion significantly improved (decreased) in children receiving AG for 10 days but not in those receiving glycine controls. AG significantly increased cumulative change over 120 days in WHZ and WAZ scores but not HAZ scores after adjustment for age and season in comparison with the placebo glycine group. **CONCLUSIONS:** Children tolerated AG-supplemented enteral formula well, and it significantly improved cumulative WHZ and WAZ over 120 days in comparison with children in the placebo glycine group. The data also suggested a beneficial effect of AG in the barrier function paracellular pathway, albeit with reduced mannitol excretion. Thus, although the effect of AG on reduced mannitol concentration requires clarification, AG appears to improve nutrition and barrier function.

J Pediatr Gastroenterol Nutr. 2006 Oct;43(4):525-32.

Growth and change in blood haemoglobin concentration among underweight Malawian infants receiving fortified spreads for 12 weeks: a preliminary trial.

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OBJECTIVE: Fortified spreads (FSs) have proven effective in the rehabilitation of severely malnourished children. We examined acceptability, growth and change in blood haemoglobin (Hb) concentration among moderately underweight ambulatory infants given FS. **METHODS:** This was a randomised, controlled, parallel-group, investigator-blind clinical trial in rural Malawi. Six- to 17-month-old underweight infants (weight for age < -2), whose weight was greater than 5.5 kg and weight-for-height z score greater than -3 received for 12 weeks at home

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1 of 8 food supplementation schemes: nothing, 5, 25, 50, or 75 g/day milk-based FS or 25, 50, or 75 g/day soy-based FS. Outcome measures included change in weight, length and blood Hb concentration. RESULTS: A total of 126 infants started and 125 completed the intervention. All infants accepted the spread well, and no intolerance was recorded. Average weight and length gains were higher among infants receiving daily 25 to 75 g FS than among those receiving only 0 to 5 g FS. Mean Hb concentration remained unchanged among unsupplemented controls but increased by 10 to 17 g/L among infants receiving any FS. All average gains were largest among infants receiving 50 g of FS daily: mean difference (95% confidence interval) in the 12-week gain between infants in 50 g milk-based FS group and the unsupplemented group was 290 g (range, -130 to 700 g), 0.9 cm (range, -0.3 to 2.2 cm), and 17 g/L (range, 0 to 34 g/L) for weight, length and blood Hb concentration, respectively. In soy- vs milk-based FS groups, average outcomes were comparable. CONCLUSIONS: Supplementation with 25 to 75 g/day of highly fortified spread is feasible and may promote growth and alleviate anaemia among moderately malnourished infants. Further trials should test this hypothesis.

Comment

Use of high density fortified spreads is a new approach to delivering multiple micronutrients and calories to malnourished or high risk children. High nutrient dense spreads have powdered ingredients which are embedded in a base being mixtures of peanut, whey powder, soy-bean powder, vegetable fat and sugar. The fat protects vitamins against oxidation and increases the product shelf life. Spreads have a very low humidity and bacteria do not grow in them. These are a supplement to the traditional food for malnourished children being skimmed milk, oil and sugar with added vitamins, which need to be carefully prepared and are prone to bacterial contamination if not used promptly or if refrigeration is inadequate. See also Brit J Nutrition, 2001; 85:s2:175-179 and Am J Clin Nutri, 2004; 80:973-981

Measles

BMJ. 2006 Dec 16;333(7581):1245. Epub 2006 Oct 23.

<http://www.bmj.com/cgi/content/full/333/7581/1245>

Prophylactic antibiotics to prevent pneumonia and other complications after measles: community based randomised double blind placebo controlled trial in Guinea-Bissau.

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OBJECTIVE: To investigate whether prophylactic antibiotics can prevent complications of measles. DESIGN: Community based, randomised, double blind, placebo controlled trial. SETTING: Bandim Health Project study area in Bissau, Guinea-Bissau, west Africa. PARTICIPANTS: 84 patients with measles during a measles epidemic in Bissau in 1998 (fewer than originally planned owing to interruption by war). INTERVENTIONS: Sulfamethoxazole-trimethoprim (co-trimoxazole) or placebo for seven days. MAIN OUTCOME MEASURES: Pneumonia and admission to hospital. Also weight change during the first month of infection, diarrhoea, severe fever, oral thrush, stomatitis, conjunctivitis, and otitis media. RESULTS: The median age of the patients with measles was 5.4 (range 0.49-24.8) years. One of 46 participants

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who received co-trimoxazole developed pneumonia, in contrast to six of 38 participants who received placebo (odds ratio 0.08 (95% confidence interval 0 to 0.56), adjusted for age group). The number needed to treat was 7 (4 to 48). All three participants admitted to hospital had received placebo (P=0.09). The weight gain during the first month after inclusion was 15 (2-29) g/day in the placebo group and 32 (23-42) g/day in the co-trimoxazole group (P=0.04, adjusted for age group, weight for age at inclusion, measles vaccination status, and duration of disease). Significantly less conjunctivitis occurred among recipients of co-trimoxazole than placebo, as well as a non-significant tendency to less diarrhoea, severe fever, oral thrush, and stomatitis. Complications of otitis media were the same in the two groups. **CONCLUSIONS:** The group that received prophylactic antibiotics had less pneumonia and conjunctivitis and had significantly higher weight gains in the month after inclusion. The results indicate that prophylactic antibiotics may have an important role in the management of measles infection in low income countries. **TRIAL REGISTRATION:** Clinical trials NCT001168532.

Comment

This is an important study which addresses a previous Cochrane review (Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001477), which found weak evidence for giving antibiotics in measles. The evidence until now has only supported giving antibiotics in children who have clinical signs of pneumonia. This study from Guinea-Bissau suggests that cotrimoxazole is effective in preventing measles-related pneumonia, conjunctivitis and improving weight gain. Although too small to demonstrate an impact on mortality, an observational study from Senegal showed a two-fold reduction in mortality after prophylactic antibiotics were introduced (Pediatr Infect Dis J 1995;14:695-6)

Neonatal and maternal care

BJOG. 2007 Jul;114(7):802-11.

Randomised controlled trial of two antenatal care models in rural Zimbabwe.

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OBJECTIVE: To compare a five-visit antenatal care (ANC) model with specified goals with the standard model in a rural area in Zimbabwe. **DESIGN:** Cluster randomised controlled trial with the clinic as the randomisation unit. **SETTING:** Primary care setting in a developing country where care was provided by nurse-midwives. **POPULATION:** Women booking for ANC in the clinics were eligible. **MAIN OUTCOME MEASURES:** Number of antenatal visits, antepartum and intrapartum referrals, utilization of health centre for delivery and perinatal outcomes. **METHODS:** Twenty-three rural health centres were stratified prior to random allocation to the new (n = 11) or standard (n = 12) model of care. **RESULTS:** We recruited 13,517 women (new, n = 6897 and standard, n = 6620) in the study, and 78% (10,572) of their pregnancy records were retrieved. There was no difference in median maternal age, parity and gestational age at booking between women in the standard model and those in the new model. The median number

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of visits was four for both models. The proportion of women with five or less visits was 77% in the new and 69% in the standard model (OR 1.5; 95% CI 1.08-2.2). The likelihood of haemoglobin testing was higher in the new model (OR 2.4; 95% CI 1.0-5.7) but unchanged for syphilis testing. There were fewer intrapartum transfers (5.4 versus 7.9% [OR 0.66; 95% CI 0.44-0.98]) in the new model but no difference in antepartum or postpartum transfers. There was no difference in rates of preterm delivery or low birthweight. The perinatal mortality was 25/1000 in standard model and 28/1000 in new model. **CONCLUSION:** In Gutu district, a focused five-visit schedule did not change the number of contacts but was more effective as expressed by increased adherence to procedures and better use of institutional health care.

Matern Child Nutr. 2007 Jul;3(3):174-85.

Preterm delivery but not intrauterine growth retardation is associated with young maternal age among primiparae in rural Nepal.

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Pregnancy during adolescence is associated with adverse birth outcomes, including preterm delivery and low birthweight. The nutrient availability to the fetus may be limited if the mother is still growing. This research aims to study the effects of pregnancy during adolescence in a nutritionally poor environment in rural Nepal. This study utilized data from a randomized controlled trial of micronutrient supplementation during pregnancy in south-eastern Nepal. Women of parity 0 or 1 and of age ≤ 25 years who gave birth to a singleton liveborn infant who was measured within 72 h of delivery were included (n = 1393). There was no difference in the risk of low birthweight (OR = 0.96; 95% CI = 0.90-1.02) or small for gestational age (OR = 1.01; 95% CI = 0.94-1.08) per year of increasing maternal age among primiparae. Young maternal age did not affect the anthropometry or gestational age of the offspring of parity 1 women. Each year of increasing maternal age among primiparae was associated with increases in birth length (0.07 cm; 95% CI = -0.01 to 0.16), head (0.05 cm; 95% CI = 0.01-0.09) and chest circumference (0.07 cm; 95% CI = 0.01-0.12), but not weight (9.0 g; 95% CI = -2.1 to 21.8) of their offspring. Young maternal age was associated with an increased risk of preterm delivery among primiparae (OR = 2.07; 95% CI = 1.26-3.38) that occurred at an age cut-off of ≤ 18 years relative to those 19-25 years. Thus, we conclude that young maternal age (≤ 18 years) increased the risk of preterm delivery, but not intrauterine growth retardation, for the first but not second liveborn infant.

Nosocomial infection

J Clin Nurs. 2007 Jun;16(6):1173-9.

Effectiveness of hand-washing teaching programs for families of children in paediatric intensive care units.

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AIMS: The authors developed a video-centred teaching program based on social learning principles to demonstrate hand-washing technique. A comparison was made between families who viewed the video and families who were taught the same techniques with the aid of an illustrated poster in terms of compliance and improvement in hand-washing skills.

BACKGROUND: Nosocomial infections are a significant cause of morbidity and mortality in paediatric intensive care unit patients. Hand hygiene is considered the most important preventive action against hospital-acquired infections. A number of studies have shown that increased compliance with hand-washing guidelines for health-care workers leads to decreases in nosocomial infection rates. Furthermore, recommendations have been made to ensure that parents who visit their children in intensive care units wash their hands first. **STUDY DESIGN:** Quasi-experimental time series. Compliance and accuracy measurements were collected during one to five visits following the initial teaching intervention. **METHODS:** A total of 123 families, who visited paediatric intensive care units, were recruited and assigned to two groups - one experimental (61 families) and the other a comparison group (62). Participants in the comparison group were taught hand-washing skills using simple illustrations. A 20-item hand-washing checklist was used to examine hand-washing compliance and accuracy. **RESULTS:** No significant differences were noted in terms of demographics between the two groups. Results from a general estimated equation analysis showed that families in the experimental group had higher compliance and accuracy scores at statistically significant levels. **CONCLUSION:** The video-based teaching program was effective in increasing compliance and accuracy with a hand-washing policy among families with children in intensive care units. **RELEVANCE TO CLINICAL PRACTICE:** The education program is a simple, low-cost, low technology intervention for substantially reducing the incidence of nosocomial infection.

Nutrition

(See also Neonatal care, Vitamin A)

Food Nutr Bull. 2006 Sep;27(3):203-10.

Impact of a multiple-micronutrient food supplement on the nutritional status of schoolchildren.

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BACKGROUND: Multiple-micronutrient deficiencies exist in many developing nations. A system to deliver multiple micronutrients effectively would be of value in these countries.

OBJECTIVE: To evaluate the delivery of multiple micronutrients through the food route. The goal was to test the stability of the supplement during cooking and storage and then to test its bioefficacy and bioavailability in residential schoolchildren 5 to 15 years of age. **METHODS:** A pre- and post-test design was used to study children 5 to 15 years of age, with an experimental and a control group. The experimental group (n=211) consisted of children from two residential schools, and the control group (n=202) consisted of children from three residential schools. The experimental group received a micronutrient supplement containing vitamin A, vitamin B2,

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vitamin B6 vitamin B12, folic acid, niacin, calcium pantothenate, vitamin C, vitamin E, iron, lysine, and calcium daily for 9 months. There was no nutritional intervention in the control group. Children in the experimental and control groups were matched by socioeconomic status, age, and eating habits at baseline. All of the children in the experimental and control schools were dewormed at baseline, after 4 months, and at the endpoint. Biochemical measurements (hemoglobin, serum vitamin A, serum vitamin E, serum vitamin B12, and serum folic acid) were measured at baseline, after 4 months, and at the endpoint (after 9 months). The heights and weights of the children were also measured at baseline and endpoint. Serum vitamins A and E were measured in a subsample of 50% and vitamin B12 and serum folic acid measured in a subsample of 25% of the children. **RESULTS:** In the experimental group, the mean gains in hemoglobin, serum vitamin A, serum vitamin E, serum vitamin B12, and serum folic acid over 9 months were 0.393 g/dL, 6.0375 microg/dL, 1037.45 microg/dL, 687.604 pg/mL, and 1.864 ng/mL, respectively. In the control group, the mean losses in hemoglobin and serum vitamin A over 9 months were 0.9556 g/dL and 10.0641 microg/dL, respectively, and the mean gains in serum vitamin E, vitamin B12, and folic acid were 903.52 microg/dL, 233.283 pg/mL, and 0.0279 ng/mL. The mean gain in all biochemical measurements was significantly higher ($p < .05$) in the experimental group than in the control group. **CONCLUSIONS:** Vitamin A, vitamin E, vitamin B12, folic acid, and iron are bioavailable from the multiple-micronutrient food supplement used in this study. This method of micronutrient delivery has been beneficial. We believe the study intervention was beneficial because of small doses of the micronutrients added but delivered many times through meals throughout the day, over a period of 9 months.

Am J Clin Nutr. 2007 Apr;85(4):1127-33.

Community-level micronutrient fortification of a food supplement in India: a controlled trial in preschool children aged 36-66 mo.

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BACKGROUND: Children participating in the Integrated Child Development Service (ICDS) in India have high rates of iron and vitamin A deficiency. **OBJECTIVE:** The objective was to assess the efficacy of a premix fortified with iron and vitamin A and added at the community level to prepared khichdi, a rice and dal mixture, in increasing iron and vitamin A stores and decreasing the prevalence of iron deficiency, anemia, and vitamin A deficiency. **DESIGN:** This cluster, randomized, double-blind, controlled trial was initiated in 30 Anganwadi centers (daycare centers) in West Bengal state, India. Children aged 36-66 mo ($n = 516$) attending village-based ICDS centers were randomly assigned to receive either a fortified or a nonfortified premix for 24 wk. Blood was drawn at 0 and 24 wk by venipuncture for the measurement of hemoglobin, serum ferritin, and serum retinol. **RESULTS:** The change in the hemoglobin concentration of anemic children was significantly different between fortified and nonfortified khichdi groups ($P < 0.001$). Prevalence rates of anemia, iron deficiency, and iron deficiency anemia were significantly lower after 24 wk in the fortified-khichdi group than in the nonfortified-khichdi group ($P < 0.001$). There were no significant differences in serum retinol concentrations or in the prevalence of vitamin A deficiency between the fortified- and nonfortified-khichdi groups. **CONCLUSION:** A premix fortified with iron, vitamin A, and folic

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acid and added to supplementary food at the community level can be effective at increasing iron stores and reducing the prevalence of iron deficiency and anemia.

Am J Clin Nutr. 2007 Apr;85(4):1041-9.

Carotene-rich plant foods ingested with minimal dietary fat enhance the total-body vitamin A pool size in Filipino schoolchildren as assessed by stable-isotope-dilution methodology.

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BACKGROUND: Strategies for improving the vitamin A status of vulnerable populations are needed. **OBJECTIVE:** We studied the influence of the amounts of dietary fat on the effectiveness of carotene-rich plant foods in improving vitamin A status. **DESIGN:** Schoolchildren aged 9-12 y were fed standardized meals 3 times/d, 5 d/wk, for 9 wk. The meals provided 4.2 mg provitamin A carotenoids/d (mainly beta-carotene) from yellow and green leafy vegetables [carrots, pechay (bok choy), squash, and kangkong (swamp cabbage)] and 7, 15, or 29 g fat/d (2.4, 5, or 10 g fat/meal) in groups A, B, and C (n = 39, 39, and 38, respectively). Other self-selected foods eaten were recorded daily. Before and after the intervention, total-body vitamin A pool sizes and liver vitamin A concentrations were measured with the deuterated-retinol-dilution method; serum retinol and carotenoid concentrations were measured by HPLC. **RESULTS:** Similar increases in mean serum beta-carotene (5-fold), alpha-carotene (19-fold), and beta-cryptoxanthin (2-fold) concentrations; total-body vitamin A pool size (2-fold); and liver vitamin A (2-fold) concentrations were observed after 9 wk in the 3 study groups; mean serum retinol concentrations did not change significantly. The total daily beta-carotene intake from study meals plus self-selected foods was similar between the 3 groups and was 14 times the usual intake; total fat intake was 0.9, 1.4, or 2.0 times the usual intake in groups A, B, and C, respectively. The overall prevalence of low liver vitamin A (<0.07 $\mu\text{mol/g}$) decreased from 35% to 7%. **CONCLUSIONS:** Carotene-rich yellow and green leafy vegetables, when ingested with minimal fat, enhance serum carotenoids and the total-body vitamin A pool size and can restore low liver vitamin A concentrations to normal concentrations.

J Nutr. 2007 Apr;137(4):1119-23.

Meat supplementation improves growth, cognitive, and behavioral outcomes in Kenyan children.

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A randomized, controlled school feeding study was conducted in rural Embu District, Kenya to test for a causal link between animal-source food intake and changes in micronutrient nutrition and growth, cognitive, and behavioral outcomes. Twelve primary schools were randomly assigned to 1 of 4 groups. Children in Standard I classes received the local plant-based dish githeri as a midmorning school snack supplemented with meat, milk, or fat added to equalize energy content in all feedings. The Control children received no feedings but participated in data collection. Main outcome measures assessed at baseline and longitudinally were 24-h food intake recall, anthropometry, cognitive function, physical activity, and behaviors during school free play. For cognitive function, the Meat group showed the steepest rate of increase on Raven's Progressive Matrices scores and in zone-wide school end-term total and arithmetic test scores. The Plain githeri and Meat groups performed better over time than the Milk and Control groups ($P < 0.02-0.03$) on arithmetic tests. The Meat group showed the greatest increase in percentage time in high levels of physical activity and in initiative and leadership behaviors compared with all other groups. For growth, in the Milk group only younger and stunted children showed a greater rate of gain in height. The Meat group showed near doubling of upper midarm muscle area, and the Milk group a smaller degree of increase. This is the first randomized, controlled feeding study to examine the effect of meat- vs. milk- vs. plant-based snacks on functional outcomes in children.

Asia Pac J Clin Nutr. 2007;16(1):84-93.

Intervention with traditional food as a major source of energy, protein, iron, vitamin C and vitamin A for rural Dalit mothers and young children in Andhra Pradesh, South India.

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Intakes of energy, protein, iron and vitamin A in India are usually reported as inadequate. Recognizing that traditional food systems are sustainable, high in species variety, and have rich nutrient sources, we compared dietary intakes and nutrient sources of Dalit mothers and their children living in villages with and without an intervention based on improved access to the traditional Dalit food system. 24-hour recalls were conducted with Dalit mothers and their children aged 6-39 months during summer and rainy seasons in 2003. We found that mothers from intervention villages had significantly higher intakes of energy (mean \pm SD: 12,197 \pm 3,515 kJ vs. 11,172 \pm 3,352 kJ; $p = 0.02$) and protein (77.5 \pm 25.1 g vs. 71.1 \pm 25.2 g; $p = 0.05$) in summer, and higher intakes of energy (11,168 \pm 3,335 kJ vs. 10,168 \pm 3,730 kJ; $p = 0.04$), protein (68.9 \pm 22.6 g vs. 60.4 \pm 23.8 g; $p < 0.01$) and iron (15.8 \pm 6.6 mg vs. 13.7 \pm 9.1 mg; $p < 0.01$) during rainy season. There were no differences in children's intakes between intervention and control villages. In mothers, sorghum contributed 29% of energy, 33% of protein and 53% of iron, and green leafy vegetables contributed 21% of vitamin C and 38% of vitamin A. Our results indicate that traditional food such as sorghum, pulses and green leafy vegetables are major sources of energy, protein, iron, vitamin C and vitamin A, and that mothers from villages with the traditional food intervention had higher intakes of energy, protein and iron.

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J Pediatr Gastroenterol Nutr. 2007 Jan;44(1):136-42.

Double-blind, placebo-controlled trial comparing effects of supplementation of two micronutrient sprinkles on fatty acid status in Cambodian infants.

Agostoni C, Giovannini M, Sala D, Usuelli M, Livio L, Francescato G, Braga M, Riva E, Martiello A, Colombo C, Marangoni F, Galli C.

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BACKGROUND: Infants in developing countries require early dietary interventions to prevent nutritional deficiencies, above all protein, energy, iron and zinc. To what extent these interventions may affect the fatty acid (FA) status is still unknown. **OBJECTIVES:** To examine and compare the effects of 2 micronutrient "sprinkles" supplementations (iron 12.5 mg + folic acid 150 microg, iron/folate and iron 12.5 mg + folic acid 150 microg + zinc 5 mg + vitamins A, C and D3, mineral/micronutrient [MMN]) versus placebo on the FA status of Cambodian infants. **METHODS:** A total of 204 infants age 6 mo and living in Kompong Chhnang Province, Cambodia, were randomly assigned to receive daily supplementation of MMN (n = 68) and iron/folate (n = 68) or placebo (n = 68) for a 12-mo period in powder form as sprinkles. At the end of the intervention period, FAs in the range of 16 to 24 C were determined in blood drops absorbed on a strip collected from 182 subjects, and values among the 3 intervention subgroups and those of 21 Italian 18-mo-old, normal-growing infants as the reference group were compared. **RESULTS:** At the end of the supplementation trial, higher levels of the 2 essential FAs (EFAs) (linoleic acid, 18:2n-6, and alpha-linolenic acid, 18:3n-3) were found in the MMN group. No differences occurred for the major longer chain derivatives of both EFAs arachidonic acid (20:4n-6) and docosahexaenoic acid (22:6n-3). In MMN supplemented Cambodians, blood levels of linoleic acid approached those of Italian infants, and in addition their alpha-linolenic acid levels were improved. Cambodian infants, mostly still breast-fed through the second year of life, showed significantly higher levels of long-chain derivatives of both the n-6 and the n-3 series compared with Italians. **CONCLUSIONS:** Supplementation with iron, folic acid, zinc and vitamins was associated with an increase of linoleic acid and alpha-linolenic acid levels in Cambodian infants versus placebo, without significant changes in the concentrations of their longer chain derivatives, resulting in a FA status closer to Italian counterparts for the essential polyunsaturated FA levels. The iron/folate-treated infants showed no differences compared with the other 2 groups. Studies are needed to differentiate the potential effects of the supplemented micronutrients on the FA status.

Int J Food Sci Nutr. 2006 Nov-Dec;57(7-8):470-80.

Plasma cobalamin and folate and their metabolic markers methylmalonic acid and total homocysteine among Egyptian children before and after nutritional supplementation with the probiotic bacteria *Lactobacillus acidophilus* in yoghurt matrix.

Mohammad MA, Molloy A, Scott J, Hussein L.

Randomised trials in child health in developing countries 2006-67

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OBJECTIVE: To evaluate the biopotency of the viable probiotic *Lactobacillus acidophilus* (La1) in yoghurt matrix consumed by Egyptian children on their plasma vitamin B12 and folate levels, and their metabolic markers methylmalonic acid (MMA) and total homocysteine (t-Hcy). **METHODS:** A randomized nutritional supplementation trial (42 days duration) was performed in free-living children of both sexes (11 years old). The La1 in yoghurt matrix was administered to provide 1012 colony-forming units/subject/day. Blood sampling for the analysis of plasma vitamin B12, folate and t-Hcy was performed by standardized methods. Five-hour urine collection was used for the analysis of MMA and t-Hcy. **RESULTS:** Initially 33.3% of the children presented with biochemical vitamin B12 deficiency (<208 pg/ml), while one-fifth (21%) were biochemically deficient in folate (<3 ng/ml folate/ml plasma or 0.68 nmol/l). Fifty percent of the children presented with high plasma t-Hcy (>15.0 micromol/l). The daily consumption of the probiotic La1 yoghurt for 42 days significantly improved the mean levels of plasma vitamin B12 (P<0.05) and folate (P<0.01) among the studied children compared with the respective baseline data. On the other hand, the average levels of plasma t-Hcy and urinary MMA decreased significantly (P<0.05) at the termination of the 42-day nutritional supplementation, compared with the respective initial mean levels. The consumption of the probiotic yoghurt was also associated with a significant (chi2=8.0; P<0.01) reduction in the percentage prevalence of anemia (hemoglobin <120 g/l). **CONCLUSION:** The long-term ingestion of viable probiotic La1 potentially promoted the overall nutritional status of the studied children.

BMJ. 2007 Jan 20;334(7585):140. Epub 2006 Nov 28.

<http://www.bmj.com/cgi/content/full/334/7585/140>

Effects of fortified milk on morbidity in young children in north India: community based, randomised, double masked placebo controlled trial.

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OBJECTIVE: To evaluate the efficacy of milk fortified with specific multiple micronutrients on morbidity in children compared with the same milk without fortification. **DESIGN:** Community based, double masked, individually randomised trial. **SETTING:** Peri-urban settlement in north India. **PARTICIPANTS:** Children (n=633) aged 1-3 randomly allocated to receive fortified milk (n=316) or control milk (n=317). **INTERVENTION:** One year of fortified milk providing additional 7.8 mg zinc, 9.6 mg iron, 4.2 microg selenium, 0.27 mg copper, 156 microg vitamin A, 40.2 mg vitamin C, 7.5 mg vitamin E per day (three feeds). **MAIN OUTCOME MEASURES:** Days with severe illnesses, incidence and prevalence of diarrhoea, and acute lower respiratory illness. **RESULTS:** Study groups were comparable at baseline; compliance in the groups was similar. Mean number of episodes of diarrhoea per child was 4.46 (SD 3.8) in the intervention (fortified milk) group and 5.36 (SD 4.1) in the control group. Mean number of episodes of acute lower respiratory illness was 0.62 (SD 1.1) and 0.83 (SD 1.4), respectively. The fortified milk reduced the odds for days with severe illnesses by 15% (95% confidence interval 5% to 24%), the incidence of diarrhoea by 18% (7% to 27%), and the incidence of acute

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lower respiratory illness by 26% (3% to 43%). Consistently greater beneficial effects were observed in children aged < or =24 months than in older children. CONCLUSION: Milk is well accepted as a means of delivery of micronutrients. Consumption of milk fortified with specific micronutrients can significantly reduce the burden of common morbidities among preschool children, especially in the first two years of life. TRIAL REGISTRATION: NCT00255385 [ClinicalTrials.gov].

Comment

An interesting result that shows that milk can be used to deliver iron and zinc and reduce morbidity from common infectious diseases. This is in contrast to iron supplementation programs that have tended to show increased diarrhoeal (and malaria) morbidity in children receiving iron in malaria endemic areas (see Iron deficiency).

Asia Pac J Public Health. 2006;18(2):21-5.

Effect of B vitamins-fortified foods on primary school children in Beijing.

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The objective of this study is to investigate the effect of B vitamins-fortified foods on primary school children. A controlled trial was conducted in 101 normal primary school children aged 9-11 years. They were randomly assigned to supplemental control group (S-control, n=36), riboflavin supplementation group (+riboflavin 0.625 mg/day, n=32), and B vitamin compound supplementation group (+riboflavin 0.625 mg/day, +thiamin 0.512 mg/day, +nicotinic acid 0.365 mg/day, +folic acid 0.13 mg/day, n=33) based on school classes. Urinary riboflavin excretion and erythrocyte glutathione reductase activity coefficient (EGRAC) along with erythrocyte transketolase activity (ETKA) were used to evaluate B vitamin levels in the children. AYP index, an index reflecting the brain performance ability, was chosen to assess the children's study abilities. Health education was carried out to help children and their parents adopt scientific dietary concepts. The urinary riboflavin excretion was higher in two supplementation groups (435.24 +/- 153.3 microg/g creatinine, 374.6 +/- 144.6 microg/g creatinine) than in S-control group (235.1 +/- 86.2 microg/g creatinine). Average values of EGRAC were lower in two supplementation groups (0.90 +/- 0.11, 0.80 +/- 0.10) than in S-control group (1.08 +/- 0.25). At the same time, the percentage of thiamine pyrophosphate (TPP%) decreased from 63.69 +/- 28.04 to 42.16 +/- 16.31 in B vitamin compound supplementation group. Meanwhile, AYP index increased at the end of the supplementation in two supplementation groups. B vitamins supplementation can significantly increase B vitamin level in children. Biochemical activities of riboflavin and thiamin can improve with the intake of fortified foods. The effect of B vitamin compound supplementation is better than that of single riboflavin supplementation when the effect of riboflavin's biofunction is considered. In addition, micronutrient supplementation appears to assist children's study abilities.

Oral health

Community Dent Oral Epidemiol. 2007 Jun;35(3):207-14.

Effectiveness of ART and traditional amalgam approach in restoring single-surface cavities in posterior teeth of permanent dentitions in school children after 6.3 years.

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OBJECTIVES: The Atraumatic Restorative Treatment (ART) approach was compared with the traditional amalgam (TA) approach in order to test their appropriateness to complement a preventive and educational school oral health programme in Syria. **METHODS:** Using a parallel group design, 370 and 311 grade 2 children were randomly assigned to the ART and the TA group respectively. Eight dentists placed 1117 single- and multiple-surface restorations. A modified actuarial method was used to estimate survival curves. The jackknife method was applied to calculate the standard error in the cumulative survival percentages. **RESULTS:** A statistically significant difference in cumulative survival percentages between single-surface non-occlusal ART and comparable amalgam restorations was observed after 4.3, 5.3 and 6.3 years. The survival of single-surface non-occlusal ART posterior restorations (80.2 +/- 4.9%) was statistically significantly higher than that of occlusal posterior ART restorations (64.8 +/- 3.9%) at evaluation year 6.3. There was no statistically significant difference observed between survival percentages of large (55.8 +/- 10%) and that of small (69.2 +/- 4.6%) single-surface posterior ART restorations after 6.3 years. There was an operator effect observed for single-surface ART and comparable amalgam restorations. Secondary caries was observed in 2.3% of single-surface ART restorations and in 3.7% of single-surface amalgam restorations during the 6.3 year observation period. **CONCLUSIONS:** The ART approach provided higher survival percentages for single-surface restorations than the TA approach over 6.3 years and is therefore appropriate for use in school oral health programmes. Secondary caries was only a minor reason for ART restorations to fail. An operator effect was observed for both treatment approaches.

Ophthalmology

(See also, Public health / hygiene)

Invest Ophthalmol Vis Sci. 2007 Mar;48(3):1025-31.

Cost-effectiveness of cycloplegic agents: results of a randomized controlled trial in nigerian children.

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PURPOSE: To compare the cost and effectiveness of three cycloplegic agents among Nigerian children. **METHODS:** Two hundred thirty-three children aged 4 to 15 years attending outpatient eye clinics in Nigeria were randomized to (1) 1% cyclopentolate, (2) 1% cyclopentolate and 0.5% tropicamide, or (3) 1% atropine drops in each eye (instilled at home over 3 days). Ten children were lost to follow-up, nine from the atropine group. An optometrist measured the residual accommodation (primary outcome), dilated pupil size, pupil response to light, and self-reported side effects (secondary outcomes). Caregivers were interviewed about costs incurred due to cycloplegia (primary outcome). The incremental cost effectiveness ratios (ICERs) were calculated as the difference in cost divided by the difference in effectiveness comparing two agents. The 95% confidence intervals (CI) for ICERs were estimated through bootstrapping. **RESULTS:** The atropine group had significantly lower mean residual accommodation (0.04 +/- 0.01 D [SE]), than the combined regimen (0.36 +/- 0.05 D) and cyclopentolate (0.63 +/- 0.06 D) groups ($P < 0.001$). Atropine and the combined regimen produced better results for negative response to light and dilated pupil size than cyclopentolate. Atropine was more expensive, but also more effective, than the other agents. The ICER comparing atropine to the combined regimen was 1.81 (95% CI = -6.31-15.35) and compared to cyclopentolate was 0.59 (95% CI = -3.47-5.47). The combined regimen was both more effective and less expensive than cyclopentolate alone. **CONCLUSIONS:** A combination of cyclopentolate and tropicamide should become the recommended agent for routine cycloplegic refraction in African children. The combined regimen was more effective than cyclopentolate, but not more expensive, and was preferable to atropine, since it incurred fewer losses to follow-up.

Br J Ophthalmol. 2006 Dec;90(12):1472-5. Epub 2006 Aug 17.

Corneal ulceration in south-east Asia III: prevention of fungal keratitis at the village level in south India using topical antibiotics.

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AIM: To determine whether topical antifungal prophylaxis distributed by paid village health workers (VHWs) in south India is necessary after corneal abrasion to prevent fungal keratitis in a population where half of the ulcers are fungal. **METHODS:** Two panchayaths (village administrative units in Madurai district with a combined population of 48 039 were followed prospectively for 18 months by 15 VHWs who were trained to identify post-traumatic corneal abrasions. Patients fulfilling the eligibility criteria were randomised into two groups and treated with either 1% chloramphenicol and 1% clotrimazole ointment or 1% chloramphenicol and a placebo ointment three times a day for 3 days. Patients, doctors and VHWs were blinded to treatment. **RESULTS:** During the 18-month period, 1365 people reported to VHWs with ocular injuries, of whom 374 with corneal abrasions were eligible for treatment. Of these, 368 (98.5%) abrasions healed without complications. Two patients had mild localised allergic reactions to the ointment, two dropped out and two patients in the placebo group developed microscopic culture-negative corneal stromal infiltrates that healed in 1 week with natamycin drops. **CONCLUSIONS:** Both fungal and bacterial ulcers that occur after traumatic corneal abrasions seem to be effectively prevented in a village setting using only antibiotic prophylaxis.

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Am J Trop Med Hyg. 2007 Jan;76(1):129-31.

Chlamydia on children and flies after mass antibiotic treatment for trachoma.

Lee S, Alemayehu W, Melese M, Lakew T, Lee D, Yi E, Cevallos V, Donnellan C, Zhou Z, Chidambaram JD, Gaynor BD, Whitcher JP, Lietman TM.

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There are various approaches to control trachoma. These include the elimination of the ocular strains of *Chlamydia trachomatis* that cause the disease and to decrease the spread of infection by other measures such as fly control. Here, we examined how these two are related (i.e., how treating children with antibiotics affects carriage of *Chlamydia* by flies). Flies were collected in villages that had received mass oral azithromycin distribution and were compared with flies in untreated villages. Polymerase chain reaction (PCR) was performed to detect chlamydial DNA on the flies. Conjunctival swabs were also taken to assay for chlamydial prevalence in the children. *Chlamydia* was found on 23% of the flies in the untreated villages but only 0.3% in treated villages. Prevalence of trachoma in children proved to be an excellent predictor of the prevalence on flies (correlation coefficient, 0.89). Thus, treating children with antibiotics may drastically reduce the role of flies as a vector.

Lancet. 2006 Aug 12;368(9535):596-600.

Intensive insecticide spraying for fly control after mass antibiotic treatment for trachoma in a hyperendemic setting: a randomised trial.

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BACKGROUND: There are no data on the cumulative effect of fly control and antibiotic distribution on trachoma in hyperendemic communities. We sought to determine whether insecticide spray intervention after mass antibiotic treatment could reduce trachoma and ocular infection with *Chlamydia trachomatis* in hyperendemic neighbourhoods in Tanzania. **METHODS:** We did a single-blind, randomised clinical trial in 16 neighbourhoods (balozi) in Kongwa, Tanzania. All children aged 1-7 years were enrolled, with 119 children in the eight balozi of the intervention group and 183 in the eight control balozi. Children were examined at baseline, 6 months, and 1 year for clinical trachoma and ocular *C trachomatis* infection. One dose of azithromycin was offered to all residents of both intervention and control balozi after the baseline survey. Households (and surrounding areas) in the intervention group were then sprayed with insecticide throughout the ensuing year and monitored for reductions in fly counts. This study is registered at ClinicalTrials.gov, number NCT00347763. **FINDINGS:** The intervention balozi had significantly lower fly counts than controls at all monitored weeks ($p < 0.05$), apart from weeks 7-9. The trachoma rate did not differ significantly in the intervention and control balozi at 6 months post-treatment (20% vs 33%, $p = 0.07$), nor did it at 1 year (43% vs 44%, $p = 0.90$). Infection with *C trachomatis* did not differ between groups at 6 months post-treatment (9% vs 7%, $p = 0.45$). **INTERPRETATION:** Intensive insecticide spraying reduced flies

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in the environment, but our results suggest that fly reduction after mass antibiotic treatment has no added benefit on reduction of trachoma.

Comment

The above two RCTs on trachoma prevention are interesting, this negative study of insecticide spraying, and a positive study showing antibiotic treatment of children dramatically reduced the proportion of flies carrying chlamydia, and the prevalence of trachoma.

Surgical problems

Br J Anaesth. 2006 Sep;97(3):385-8. Epub 2006 Jun 23.

Efficacy of three doses of tramadol with bupivacaine for caudal analgesia in paediatric inguinal herniotomy.

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BACKGROUND: This study was designed to evaluate the analgesic efficacy of three doses of tramadol, administered caudally with bupivacaine, in providing postoperative pain relief in children. **METHODS:** Eighty children, aged between 2 and 8 yr, undergoing inguinal herniotomy were randomly allocated to receive bupivacaine 0.25% 0.75 ml kg⁻¹ (Group B; n=20), bupivacaine 0.25% 0.75 ml kg⁻¹ with tramadol 1 mg kg⁻¹ (Group BT1; n=20), bupivacaine 0.25% 0.75 ml kg⁻¹ with tramadol 1.5 mg kg⁻¹ (Group BT1.5; n=20), or bupivacaine 0.25% 0.75 ml kg⁻¹ with tramadol 2 mg kg⁻¹ (Group BT2; n=20) by the caudal route immediately after induction of general anaesthesia. Heart rate, arterial pressure and oxygen saturation were monitored. Postoperative pain was assessed at regular intervals for 24 h using All India Institute of Medical Sciences pain score. Analgesia was supplemented whenever pain score was ≥ 4 . Duration of analgesia and requirement for additional analgesics was noted. **RESULTS:** Duration of analgesia was longer in Group BT2 [(mean (SD) 12 (0.9) h] compared with Group B [4 (1) h], Group BT1 [8 (0.9) h], or Group BT1.5 [11 (1) h]; all $P < 0.001$. Total consumption of rescue analgesic was significantly lower in group BT2 compared with other groups ($P < 0.001$). There were no significant changes in heart rate, arterial pressure and oxygen saturation between groups. Adverse effects were not observed. **CONCLUSIONS:** Caudal tramadol 2 mg kg⁻¹, combined with bupivacaine 0.25% 0.75 ml kg⁻¹, provided longer duration of postoperative analgesia and reduced requirement for rescue analgesic compared with tramadol 1 mg kg⁻¹ or 1.5 mg kg⁻¹ in children undergoing inguinal herniotomy.

Supportive care

Res Nurs Health. 2007 Jun;30(3):320-32.

Effects of preoperative therapeutic play on outcomes of school-age children undergoing day surgery.

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The purpose of this study was to examine the effects of therapeutic play on outcomes of children undergoing day surgery. Two hundred and three children admitted for day surgery were invited to participate in a randomized controlled trial. The experimental group received therapeutic play; the control group received routine information preparation. Children in the experimental group reported significantly lower state anxiety scores in pre- and postoperative periods and exhibited fewer negative emotions at induction of anesthesia than children in the control group. No significant differences were found between the two groups in postoperative pain. The study provides some evidence that therapeutic play is effective in pre- as opposed to postsurgical management of children.

Taehan Kanho Hakhoe Chi. 2006 Dec;36(8):1301-7.

Effects of programmed information on coping behavior and emotions of mothers of young children undergoing IV procedures.

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PURPOSE: To determine the effects of provision of information on mother's problem focused coping ability during their child's intravenous procedure. **METHODS:** Data were collected from 56 mothers whose children have admitted to pediatric ward in the hospital. The participants included 27 intervention group mothers and 29 control group mothers. For the information intervention, "Programmed Information for Parental Coping before Intravenous Procedure (PIPC-IP)", video program was made based on self-regulation theory for the experimental group mothers. Mother's coping ability was measured by parental supportive behavior, parental beliefs and Profile of Mood State (POMS). **RESULTS:** Mothers who received PIPC-IP showed significantly higher levels of supportive behavior ($t = 3.55, p = .005$) and Parental Beliefs ($t = 2.95, p = .005$), but no significant difference in negative mood on POMS ($t = .15, p = .87$) compared to mothers in the control group. **CONCLUSIONS:** These results demonstrate that PIPC-IP is an effective intervention to increase the supportive behaviors and beliefs of mothers' problem focused coping ability but not the negative mood.

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J Nutr. 2006 Oct;136(10):2645-52.

Psychosocial stimulation improves the development of undernourished children in rural Bangladesh.

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Undernutrition in early childhood is associated with poor mental development and affects 45% of children in Bangladesh. Although limited evidence shows that psychosocial stimulation can reduce the deficits, no such interventions have been reported from Bangladesh. The Bangladesh Integrated Nutrition Program (BINP) has provided nutrition supplementation to undernourished children through community nutrition centers (CNCs). We added psychosocial stimulation to the treatment of undernourished children in a randomized controlled trial to assess the effects on children's development and growth and mothers' knowledge. Twenty CNCs were randomly assigned to intervention or control groups with 107 children in each group. We also studied 107 nonintervened better-nourished children from the same villages. Pre- and postintervention measurements included children's height, weight, development assessed on Bayley Scales, behavior ratings during the test, and a questionnaire on mothers' knowledge of childrearing. The intervention comprised home visits and group meetings with mothers and children for 12 mo. Intervention benefited children's mental development (4.6 +/- 2.0, P = 0.02), vocalization (0.48 +/- 0.23, P = 0.04), cooperation (0.45 +/- 0.16, P = 0.005), response-to-examiner (0.50 +/- 0.15, P = 0.001), emotional tone (0.33 +/- 0.15, P = 0.03), and mothers' knowledge (3.5 +/- 0.49, P < 0.001). At the end, undernourished controls had poorer mental (-4.6 +/- 2.0, P = 0.02) and motor (-6.6 +/- 2.2, P = 0.003) development, were more inhibited (-0.35 +/- 0.16, P = 0.03), fussier (-0.57 +/- 0.16, P < 0.001), less cooperative (-0.48 +/- 0.17, P = 0.005), and less vocal (-0.76 +/- 0.23, P = 0.001) than better-nourished children. Intervened children scored lower only in motor development (-4.4 +/- 2.3, P = 0.049). Neither group of undernourished children improved in nutritional status, indicating that treatment had no effect. In conclusion, adding child development activities to the BINP improved children's development and behavior and their mothers' knowledge; however, the lack of improvement in growth needs to be examined further.

Fam Community Health. 2006 Oct-Dec;29(4):314-9.

Impact of massage therapy on health outcomes among orphaned infants in Ecuador: results of a randomized clinical trial.

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Diarrhea is the second leading cause of death among infants and young children in the developing world. This project investigated whether therapeutic infant massage could reduce diarrheal episodes and decrease overall illness of infants. Infants living in 2 orphanages in

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Quito, Ecuador, were matched by age and randomly assigned to an experimental or a control condition. The experimental group received an intervention, daily infant massage therapy by orphanage staff or volunteers, which lasted an average of 53 days, and symptoms of illness data were documented daily by volunteers in the orphanages. Results indicated that control group infants had a 50% greater risk of having diarrhea than experimental infants (rate ratio [RR] = 1.54, 95% confidence interval [CI] = 1.18, 2.03, $P < 0.001$). Control group infants were also 11% more likely than experimental infants to experience illness of any kind (RR = 1.11, 95% CI = 0.96, 1.28, $P = 0.17$). The implications for the use of therapeutic infant massage, a remarkably inexpensive intervention, are discussed, and the need for further research is highlighted.

Comment

Although this sounds very promising in terms of reduction in diarrhoea, it is not correct to conclude that infants who did not receive massage were more likely experience illness of any kind, as the confidence intervals include 1. This may be because the study was underpowered to detect a difference, or that no difference really exists. Anyway, massage seems to have several positive effects (including improvements in the mood of mothers, see below) and it is very unlikely to be harmful.

Patient Educ Couns. 2007 Jan;65(1):34-41. Epub 2006 Jul 26.

Psychoeducational preparation of children for surgery: the importance of parental involvement.

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OBJECTIVE: To examine the effects of therapeutic play intervention on outcomes of children undergoing day surgery, and to highlight the importance of parental involvement in the psychoeducational preparation of children for surgery. **METHODS:** A randomized controlled trial, two group pre-test and repeated post-test, between subjects design was employed. Hong Kong Chinese children (7-12 years of age; n=203) admitted for elective surgery in a day surgery unit, along with their parents during a 13-month period, were invited to participate in the study. By using a simple complete randomization method, 97 of children with their parents were assigned to the experimental group receiving therapeutic play intervention, and 106 children with their parents were assigned to the control group receiving routine information preparation. **RESULTS:** The results showed that both children and their parents in the experimental group reported lower state anxiety scores in pre- and post-operative periods. Children in the experimental group exhibited fewer instances of negative emotional behaviors and parents in the experimental group reported greater satisfaction. The results, however, find no differences in children's post-operative pain between the two groups. **CONCLUSION:** The study provides empirical evidence to support the effectiveness of using therapeutic play intervention and the importance of parental involvement in the psychoeducational preparation of children for surgery. **PRACTICE IMPLICATIONS:** The findings heighten the awareness of the importance

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of integrating therapeutic play and parental involvement as essential components of holistic and quality nursing care to prepare children for surgery.

Complement Ther Clin Pract. 2006 Aug;12(3):181-5. Epub 2006 Mar 13.

Effect of massaging babies on mothers: pilot study on the changes in mood states and salivary cortisol level.

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The purpose of this pilot study was to evaluate the effects of baby massage for 3 months after delivery on mothers' mood status and salivary cortisol level. Study participants were a convenient sample of mothers who delivered their babies at a hospital in Japan, and were recruited at the time of the routine 5-6 weeks postnatal visit to the pediatric office. Thirty-nine mothers were randomly assigned to experimental and control groups. Nineteen mothers in the experimental group were examined before the first day of the baby massage, and 3 months after delivery. The psychological measurements used were profile of mood states (POMS). In the physiological measurements, the salivary cortisol level was analyzed. The result revealed that significant differences in the POMS score were seen in depression and vigor between the two groups at 3 months. There were no significant differences in the salivary cortisol levels. Baby massage was found to positively affect the mood status of the mothers. We propose that midwives and other health-care professionals should recommend mothers to do baby massage to improve their own mood status.

Tuberculosis

(See vaccines)

Typhoid

Indian J Pediatr. 2007 Jan;74(1):39-42.

<http://www.ijppediatricsindia.org/article.asp?issn=0019-5456;year=2007;volume=74;issue=1;spage=39;epage=42;aulast=Kumar>

Multidrug-resistant typhoid fever.

Kumar R, Gupta N; Shalini.

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OBJECTIVE: To study the epidemiological pattern, clinical picture, the recent trends of multidrug-resistant typhoid fever (MDRTF), and therapeutic response of ofloxacin and ceftriaxone in MDRTF. **METHODS:** The present prospective randomized controlled parallel study was conducted on 93 blood culture-proven *Salmonella typhi* children. All MDRTF cases were randomized to treatment with ofloxacin or ceftriaxone. **RESULTS:** Of 93 children, 62 (66.6%) were MDRTF. 24 cases were below 5 years, 26 between 5-10 years and 12 were above 10 years. Male to female ratio was 1.85: 1. Majority of cases came from lower middle socio-economic classes with poor personal hygiene. Fever was the main presenting symptom. Hepatomegaly and splenomegaly was present in 88% and 46% cases respectively. 19 (30.6%) cases developed complications. Mean defervescence time with ceftriaxone and ofloxacin was 4.258 and 4.968 days respectively. **CONCLUSION:** MDRTF is still emerging as serious public and therapeutic challenge. Ceftriaxone is well-tolerated and effective drug but expensive whereas ofloxacin is safe, cost-effective and therapeutic alternative in treatment of MDRTF in children with comparable efficacy to ceftriaxone.

Antimicrob Agents Chemother. 2007 Mar;51(3):819-25. Epub 2006 Dec 4.
<http://aac.asm.org/cgi/content/full/51/3/819?view=long&pmid=17145784>

Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever.

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Isolates of *Salmonella enterica* serovar Typhi that are multidrug resistant (MDR, resistant to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole) and have reduced susceptibility to fluoroquinolones (nalidixic acid resistant, Na(r)) are common in Asia. The optimum treatment for infections caused by such isolates is not established. This study compared different antimicrobial regimens for the treatment of MDR/Na(r) typhoid fever. Vietnamese children and adults with uncomplicated typhoid fever were entered into an open randomized controlled trial. Ofloxacin (20 mg/kg of body weight/day for 7 days), azithromycin (10 mg/kg/day for 7 days), and ofloxacin (15 mg/kg/day for 7 days) combined with azithromycin (10 mg/kg/day for the first 3 days) were compared. Of the 241 enrolled patients, 187 were eligible for analysis (186 *S. enterica* serovar Typhi, 1 *Salmonella enterica* serovar Paratyphi A). Eighty-seven percent (163/187) of the patients were children; of the *S. enterica* serovar Typhi isolates, 88% (165/187) were MDR and 93% (173/187) were Na(r). The clinical cure rate was 64% (40/63) with ofloxacin, 76% (47/62) with ofloxacin-azithromycin, and 82% (51/62) with azithromycin ($P = 0.053$). The mean (95% confidence interval [CI]) fever clearance

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time for patients treated with azithromycin (5.8 days [5.1 to 6.5 days]) was shorter than that for patients treated with ofloxacin-azithromycin (7.1 days [6.2 to 8.1 days]) and ofloxacin (8.2 days [7.2 to 9.2 days]) ($P < 0.001$). Positive fecal carriage immediately posttreatment was detected in 19.4% (12/62) of patients treated with ofloxacin, 6.5% (4/62) of those treated with the combination, and 1.6% (1/62) of those treated with azithromycin ($P = 0.006$). Both antibiotics were well tolerated. Uncomplicated typhoid fever due to isolates of MDR *S. enterica* serovar Typhi with reduced susceptibility to fluoroquinolones (Na(r)) can be successfully treated with a 7-day course of azithromycin.

Southeast Asian J Trop Med Public Health. 2006 May;37(3):515-22.

The feasibility of a school-based Vi polysaccharide vaccine mass immunization campaign in Hue City, central Vietnam: streamlining a typhoid fever preventive strategy.

Thiem VD, Danovaro-Holliday MC, Canh do G, Son ND, Hoa NT, Thuy DT, Ochiai RL, Lan NT, Hop TQ, Ali M, Park JK, Abu-Elyazeed R, Holliday K, Ivanoff B, Anh DD, Pang T, Donner A, Galindo CM, Trach DD, Clemens JD, Acosta CJ.

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We report the coverage, safety, and logistics of a school-based typhoid fever immunization campaign that took place in Hue City, central Vietnam; a typhoid fever endemic area. A cluster-randomized evaluation-blinded controlled trial was designed where 68 schools (cluster) were randomly allocated the single dose Vi polysaccharide vaccine (Typherix) or the active control hepatitis A vaccine (Havrix). A safety surveillance system was implemented. A total of 32,267 children were immunized with a coverage of 57.5%. Strong predictors for vaccination were attending primary schools, peri-urban location of the school, and low family income. Human resources were mainly schoolteachers and the campaign was completed in about 1 month. Most adverse events reported were mild. Safe injection and safe sharp-waste disposal practices were followed. A typhoid fever school-based immunization campaign was safe and logistically possible. Coverage was moderate and can be interpreted as the minimum that could have been achievable because individual written informed consent procedures were sought for the first time in Hue City and the trial nature of the campaign. The lessons learned, together with cost-effectiveness results to be obtained by the end of follow-up period, will hopefully accelerate the introduction of Vi typhoid fever vaccine in Vietnam.

Vaccines

(See also malaria, typhoid)

Pediatr Infect Dis J. 2007 Mar;26(3):247-52.

Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau.

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BACKGROUND: The 2-fold increase in female mortality after high-titer measles vaccine may have occurred because many children received diphtheria-tetanus-pertussis (DTP) vaccine or inactivated polio vaccine (IPV) after high-titer measles vaccine. **OBJECTIVE:** We examined whether DTP vaccine and IPV were associated with increased female mortality when they were the most recent vaccine administered to children who had not received measles vaccine. **Setting and Design:** IPV was used as a control vaccine in 4 randomized trials of early measles vaccination (MV) with enrollment at 4-6 months of age conducted in Guinea-Bissau. Many children had not received all 3 DTP vaccinations before enrollment, and therefore received DTP after IPV or MV. We examined whether DTP vaccination status at enrollment affected the female-male mortality ratio. **Population:** 9544 children enrolled in 4 trials. **Main outcome measure:** The female-male mortality ratio in different vaccine groups. **RESULTS:** Females had a higher mortality rate than males among children randomized to receive IPV (mortality rate ratio [MR] 1.52, 95% CI 1.02-2.28), but females had a similar mortality rate to males among children randomized to receive MV (MR 1.01, 0.69-1.46) and among children in the IPV group after they had received MV at 9 months of age or later (MR 0.88, 0.68-1.14). Children who had not received a third dose of DTP before enrollment (and were likely to receive DTP after MV or IPV) tended to have a higher mortality than children who had received all 3 doses of DTP (MR 1.30, 0.97-1.73). This effect was seen only among girls (MR 1.61, 1.08-2.40) and not among boys (MR 1.02, 0.67-1.54). Girls had a lower mortality when MV was the most recent vaccine received rather than DTP or IPV (MR 0.49, 0.28-0.87). **CONCLUSIONS:** Randomization to IPV was associated with higher female than male mortality. However, the increased female mortality might result from additional doses of DTP received after enrollment and before measles vaccination.

Comment

The findings from many studies in Guinea Bissau on the non-specific effects of measles (highly beneficial) and other vaccines (mixed) are very important, and there is an urgent need to consider carefully the results and try to replicate them elsewhere.

Vaccine. 2007 Apr 20;25(16):3118-23. Epub 2007 Jan 22.

Randomized, double-blind, multicenter study of the immunogenicity and reactogenicity of 17DD and WHO 17D-213/77 yellow fever vaccines in children: implications for the Brazilian National Immunization Program.

Collaborative Group for Studies with Yellow Fever Vaccine.

Vaccines against yellow fever currently recommended by the World Health Organization contain either virus sub-strains 17D or 17DD. In adults, the 17DD vaccine demonstrated high seroconversion and similar performance to vaccines manufactured with the WHO 17D-213/77 seed-lot. In another study, 17DD vaccine showed lower seroconversion rates in children younger than 2 years. Data also suggested lower seroconversion with simultaneous application of measles vaccine. This finding in very young children is not consistent with data from studies

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with 17D vaccines. A multicenter, randomized, double-blind clinical trial was designed (1) to compare the immunogenicity and reactogenicity of two yellow fever vaccines: 17DD (licensed product) and 17D-213/77 (investigational product) in children aged 9-23 months; (2) to assess the effect of simultaneous administration of yellow fever and the measles-mumps-rubella vaccines; and (3) to investigate the interference of maternal antibodies in the response to yellow fever vaccination. The anticipated implications of the results are changes in vaccine sub-strains used in manufacturing YF vaccine used in several countries and changes in the yellow fever vaccination schedule recommendations in national immunization programs.

Hum Vaccin. 2005 Nov-Dec;1(6):228-31. Epub 2005 Nov 7.

<http://www.landesbioscience.com/journals/vaccines/article/2301>

Safety and immunogenicity of a meningococcal (Groups A, C, Y, W-135) polysaccharide diphtheria toxoid conjugate vaccine in healthy children aged 2 to 10 years in Chile.

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Immune responses to meningococcal conjugate (Menactra; MCV-4) and plain polysaccharide (Menomune-A/C/Y/W-135; PSV-4) vaccines against serogroups A, C, Y, and W-135 were assessed in 220 of 1037 Chilean children aged 2 to 10 years participating in a comparative safety trial. Both vaccines were generally well tolerated. Geometric mean serum bactericidal antibody (SBA) titers 28 days postvaccination were comparable in both groups for all four serogroups. Seroconversion was evident in > 97% of MCV-4 and > 90% of PSV-4 vaccinees who tested seronegative at baseline. Menactra safely induced broad and robust immune responses against serogroups A, C, Y and W-135 in this population.

Pediatr Infect Dis J. 2006 Aug;25(8):706-12.

Reactogenicity and immunogenicity profiles of a novel pentavalent diphtheria-tetanus-whole cell pertussis-hepatitis B and Haemophilus influenzae type B vaccine: a randomized dose-ranging trial of the Hib tetanus-conjugate content.

Hla KH, Thein SA, Aye A, Han HH, Bock HL, David MP, Schuerman L.

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BACKGROUND: Combined vaccines containing diphtheria-tetanus-pertussis whole-cell (DTPw), Haemophilus influenzae type b (Hib), and hepatitis-B vaccines are essential for the continuing success of vaccination programs in developing nations. This randomized, dose-ranging study assessed the immunogenicity and reactogenicity of primary and booster

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vaccination with pentavalent DTPw-HBV/Hib vaccines containing 10, 5 or 2.5 microg of polyribosylribitol phosphate (PRP) conjugated to tetanus toxoid (trials Hib-052/064). **METHODS:** Six hundred eighty infants were randomized to receive one of 5 vaccine combinations at 6, 10, and 14 weeks of age. Of these, 351 received the same vaccine at 15-24 months of age. The immune response was evaluated on blood samples collected 1 month after the 3-dose primary course and before and 6 weeks after the booster dose. Reactogenicity was assessed during a 4-day period after each vaccine dose using diary cards. **RESULTS:** After primary vaccination, all subjects had seroprotective anti-PRP antibody concentrations ($>$ or $=$ 0.15 microg/mL) and $>$ 95% had concentrations $>$ or $=$ 1.0 microg/mL, irrespective of the PRP dose administered. Anti-PRP antibody avidity after primary vaccination and antibody persistence until the second year of life were similar among groups. The booster dose induced marked increases in anti-PRP antibody GMCs and antibody avidity, indicative of effective priming and the presence of immune memory. All vaccination regimens elicited good immune responses and comparable antibody persistence to the other vaccine antigens, with significant increases in all antibody concentrations observed after boosting. All vaccination regimens were safe, with similar overall reactogenicity profiles. **CONCLUSION:** Hib conjugate vaccines containing reduced amounts of PRP can be effectively combined with the licensed DTPw-HBV vaccine to provide protection against 5 major childhood pathogens in a single injection.

Comment

*This trial supports previous ones (Nicol M, et al. *Pediatr Infect Dis J*, 2002;21:138-41 and Campbell JD et al. *Pediatr Infect Dis J*, 2002;21:822-826) that suggest that fractional doses of commercially available Hib vaccine provide an effective immune response.*

Trop Med Int Health. 2007 Feb;12(2):224-9.

Revaccination with Bacillus Calmette-Guerin (BCG) vaccine does not reduce morbidity from malaria in African children.

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BACKGROUND: Studies in West Africa and elsewhere have suggested that Bacillus Calmette-Guérin (BCG) vaccine given at birth is beneficial for child survival. It is possible that this effect is mediated partly through an effect on malaria, a hypothesis supported by animal studies. We investigated whether revaccination with BCG at 19 months of age reduced morbidity from malaria. **METHOD:** In the capital of Guinea-Bissau, between January and November 2003, children who had previously received BCG vaccination and who did not have a strong reaction to tuberculin were individually randomised to either receive revaccination with BCG at the age of 19 months or to be a control. Episodes of malaria were recorded during the 2003 malaria transmission season through passive case detection at health centres in the study area and at the national hospital. Cross-sectional surveys were carried out at the beginning and at the end of the rainy season. **RESULTS:** Incidence rates of first episodes of malaria associated with any level of parasitaemia were 0.16 episodes per child-year among 713 revaccinated children and 0.12 among 720 control children [incidence rate ratio (IRR) = 1.37; 95% confidence intervals (CI): 0.84-2.25]. Results were similar when the diagnosis of malaria was based on the presence of parasitaemia $>$ 5000 parasites/microl (IRR = 1.30; 95% CI: 0.61-2.77). The incidence of all-

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cause hospitalisation was higher among BCG-revaccinated children than among controls (IRR = 2.13; 95% CI: 1.10-4.13). There were no significant differences in the prevalence of parasitaemia between the two groups of children at cross-sectional surveys. **CONCLUSION:** We found no evidence that BCG revaccination reduces morbidity from malaria.

Health Place. 2007 Sep;13(3):577-87. Epub 2007 Jan 24.

Geographic analysis of vaccine uptake in a cluster-randomized controlled trial in Hue, Vietnam.

Ali M, Thiem VD, Park JK, Ochiai RL, Canh do G, Danovaro-Holliday MC, Kaljee LM, Clemens JD, Acosta CJ.

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This paper identifies spatial patterns and predictors of vaccine uptake in a cluster-randomized controlled trial in Hue, Vietnam. Data for this study result from the integration of demographic surveillance, vaccine record, and geographic data of the study area. A multi-level cross-classified (non-hierarchical) model was used for analyzing the non-nested nature of individual's ecological data. Vaccine uptake was unevenly distributed in space and there was spatial variability among predictors of vaccine uptake. Vaccine uptake was higher among students with younger, male, or not literate family heads. Students from households with higher per-capita income were less likely to participate in the trial. Residency south of the river or further from a hospital/polyclinic was associated with higher vaccine uptake. Younger students were more likely to be vaccinated than older students in high- or low-risk areas, but not in the entire study area. The findings are important for the management of vaccine campaigns during a trial and for interpretation of disease patterns during vaccine-efficacy evaluation.

Vitamin A

Indian J Pediatr. 2007 May;74(5):443-7.

<http://www.ijppediatricsindia.org/article.asp?issn=0019-5456;year=2007;volume=74;issue=5;spage=443;epage=447;aulast=Swami>

Impact of mass supplementation of vitamin A.

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OBJECTIVE: To study the impact of mass supplementation of Vitamin A solution on morbidity due to diarrhea, Acute respiratory infection (ARI) and xerophthalmia. **METHODS:** The two

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rounds of age specific mass distribution of Vitamin A solution were undertaken during January 2000 and December 2000 respectively covering 27,642 (98.7%) and 31,762 (88.0%) children respectively out of total beneficiaries in two round of PPI in Chandigarh. A random sample of 276 children from intervention area and 252 children from control area in the age group of 1-5 yr were followed up on monthly basis for morbidity pattern for a period of nine mth. The morbidity pattern for intervention and control area children was compared to see the impact of mass supplementation of Vitamin A solution. RESULTS: The average annual episodes of diarrhea in intervention children were lower (3.9 per yr) as compared to control children (5.2 per yr) although difference was not statistically significant ($P>0.05$) except in initial month. The average annual episodes of ARI in intervention children were lower (5.1 per yr) as compared to Control children (6.0 per yr) although difference was not significant ($P>0.05$) except in initial first mth. There was significant decline in vitamin A deficiency (VAD) as no case of Bitot's spot was found in intervention children as compared to control children where the prevalence of Bitot's spot ranged from 4.3-5.08% during different visits. The mortality rate was found to be higher in control children with a death rate of 8 per 1000 children during the study period as compared to intervention children where no death was recorded. CONCLUSION: It is concluded that mass supplementation of vitamin A led to significant reduction in xerophthalmia and decline in mortality in the intervention area as compared to control area.

Am J Clin Nutr. 2007 May;85(5):1312-9.

Randomized controlled safety and efficacy trial of 2 vitamin A supplementation schedules in Tanzanian infants.

Idindili B, Masanja H, Urassa H, Bunini W, van Jaarsveld P, Aponte JJ, Kahigwa E, Mshinda H, Ross D, Schellenberg DM.

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BACKGROUND: Vitamin A supplementation reduces morbidity and mortality in children living in areas endemic for vitamin A deficiency. Routine vitamin A supplementation usually starts only at age 9 mo, but high rates of illness and mortality are seen in the first months of life. **OBJECTIVE:** The objective of the study was to evaluate the safety and efficacy of vitamin A supplementation at the same time as routine vaccination in infants aged 1-3 mo. **DESIGN:** We recruited 780 newborn infants and their mothers to a randomized double-blind controlled trial in Ifakara in southern Tanzania. In one group, mothers received 60,000 microg vitamin A palmitate shortly after delivery, and their infants received 7500 microg at the same time as vaccinations given at approximately 1, 2, and 3 mo of age. In the other group, mothers received a second 60,000-microg dose when their infant was aged 1 mo, and their infants received 15,000 microg at the same time as the routine vaccinations. VAD was defined as a modified relative dose-response test result of ≥ 0.060 . **RESULTS:** High-dose vitamin A supplementation was well tolerated. The relative risk of VAD at 6 mo in the high-dose group compared with the lower dose group was 0.91 (95% CI: 0.76, 1.09; $P=0.32$). Serum retinol and incidence of illness did not differ significantly between the 2 groups. Some vitamin A capsules degraded toward the end of the study. **CONCLUSIONS:** Doubling the doses of vitamin A to mothers and their young infants is safe but unlikely to reduce short-term morbidity or to substantially enhance the biochemical vitamin A status of infants at age 6 mo. The stability of vitamin A capsules merits further investigation.

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Asia Pac J Clin Nutr. 2007;16(1):94-102.

Impact of vitamin A supplementation on health status and absenteeism of school children in Sri Lanka.

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The objective of this study was to determine the impact of Vitamin A supplementation on health status and absenteeism of school children. A randomized double blind placebo controlled trial over a period of 13 months was conducted in a rural area of Sri Lanka involving 613 school children attending Grades 1-5 (aged 5 to 13 years). Children were assigned to either 200,000 IU of Vitamin A (n=297) or placebo (n=316) once every 4 months. Socio-demographic data were obtained at baseline, and anthropometry and haemoglobin concentrations were assessed at baseline and post intervention. Serum vitamin A concentrations were assayed by HPLC in a subgroup of children (n=193) before administration of each dose. School absenteeism was recorded. The two groups of children were similar at baseline in all variables. The subgroup of children was comparable to the main study population. The prevalence of vitamin A deficiency (< 20 microg/dL) in the subgroup of children was 8.2%. Changes in anthropometric indices and haemoglobin concentrations were similar in the two groups. The major causes for absenteeism were non-health causes and supplemented children lost a fewer number of school days due to illness than placebo children (p=0.053). Vitamin A concentrations improved with each dose and the improvement was greater with better compliance. Vitamin A supplementation with 200,000 IU every 4 months over 13 months improved vitamin A status and school attendance but not anthropometric status of these children.

Am J Clin Nutr. 2006 Sep;84(3):580-6.

Vitamin A supplementation in children with poor vitamin A and iron status increases erythropoietin and hemoglobin concentrations without changing total body iron.

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BACKGROUND: Vitamin A deficiency impairs iron metabolism; vitamin A supplementation of vitamin A-deficient populations may reduce anemia. The mechanism of these effects is unclear. In vitro and in animal models, vitamin A treatment increases the production of erythropoietin (EPO), a stimulant of erythropoiesis. **OBJECTIVE:** We measured the effect of vitamin A supplementation on hemoglobin, iron status, and circulating EPO concentrations in children with poor iron and vitamin A status. **DESIGN:** In a double-blind, randomized trial, Moroccan schoolchildren (n = 81) were given either vitamin A (200,000 IU) or placebo at

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baseline and at 5 mo. At baseline, 5 mo, and 10 mo, hemoglobin, indicators of iron and vitamin A status, and EPO were measured. RESULTS: At baseline, 54% of children were anemic; 77% had low vitamin A status. In the vitamin A group at 10 mo, serum retinol improved significantly compared with the control group ($P < 0.02$). Vitamin A treatment increased mean hemoglobin by 7 g/L ($P < 0.02$) and reduced the prevalence of anemia from 54% to 38% ($P < 0.01$). Vitamin A treatment increased mean corpuscular volume ($P < 0.001$) and decreased serum transferrin receptor ($P < 0.001$), indicating improved iron-deficient erythropoiesis. Vitamin A decreased serum ferritin ($P < 0.02$), suggesting mobilization of hepatic iron stores. Calculated from the ratio of transferrin receptor to serum ferritin, overall body iron stores remained unchanged. In the vitamin A group at 10 mo, we observed an increase in EPO ($P < 0.05$) and a decrease in the slope of the regression line of $\log_{10}(\text{EPO})$ on hemoglobin ($P < 0.01$). CONCLUSION: In children deficient in vitamin A and iron, vitamin A supplementation mobilizes iron from existing stores to support increased erythropoiesis, an effect likely mediated by increases in circulating EPO.

Public Health Nutr. 2006 Sep;9(6):808-13.

Impact of promotion of mango and liver as sources of vitamin A for young children: a pilot study in Burkina Faso.

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OBJECTIVE: To assess the effectiveness of a behaviour change approach, with or without financial support, in improving vitamin A (VA) intake and serum retinol concentration through mango and liver consumption by children. DESIGN: A parallel design (no control area) was used to assess changes in VA intake and serum retinol over a 15-week period. SETTING AND SUBJECTS: A pilot study was implemented in the Department of Kokologho, a rural area in central west Burkina Faso. One hundred and fifty children aged 2-3 years were randomly selected and assigned to two treatment groups: PA\$\$ (promotional activities and financial support) and PA (promotional activities). RESULTS: The intervention significantly increased ($P < 0.001$) total VA intake by 56% in PA\$\$ and by 50% in PA. VA intake from liver increased significantly ($P < 0.001$) from 12.7 +/- 23.5 to 155.3 +/- 56.3 microg retinol activity equivalents (RAE) in PA\$\$ and from 21.6 +/- 29.7 to 135.3 +/- 44.9 microg RAE in PA. Changes in VA intake from liver were significantly higher ($P = 0.004$) in PA\$\$ compared with PA. Mean serum retinol concentration increased significantly by 26% ($P < 0.001$) in PA\$\$ and 30% ($P < 0.001$) in PA. Changes in serum retinol concentration (0.13 micromol l(-1) in PA\$\$ vs. 0.17 micromol l(-1) and in PA) did not differ significantly ($P = 0.455$) between groups over the intervention. CONCLUSION: Promotional activities on mango and liver intake effectively increased VA intake and serum retinol concentrations. Although an additional beneficial effect of financial support on liver intake was observed, this did not translate into a further increase in serum retinol concentration.

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Nutr J. 2006 Jul 17;5:17.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16846498>

The positive impact of red palm oil in school meals on vitamin A status: study in Burkina Faso.

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BACKGROUND: Vitamin A (VA) deficiency is widespread in sub-Saharan Africa and school-age children are a vulnerable group. In Burkina Faso, the production and consumption of red palm oil (RPO) is being promoted as a food supplement for VA. The objective of the study was to assess the impact on serum retinol of adding RPO to school lunch in two test zones of Burkina Faso. **METHODS:** Over one school year, 15 ml RPO was added to individual meals 3 times a week in selected primary schools in two sites. Serum retinol was measured with HPLC at baseline and exactly 12 months later to take account of seasonality. A simple pre-post test design was used in the Kaya area (north-central Burkina), where 239 pupils from 15 intervention schools were randomly selected for the evaluation. In Bogandé (eastern Burkina), 24 schools were randomised for the controlled intervention trial: 8 negative controls (G1) with only the regular school lunch; 8 positive controls (G2) where the pupils received a single VA capsule (60 mg) at the end of the school year; and 8 schools with RPO through the school year (G3). A random sample of 128 pupils in each school group took part in the evaluation. **RESULTS:** In Kaya, serum retinol went from 0.77 +/- 0.37 micromol/L at baseline to 1.07 +/- 0.40 micromol/L one year later ($p < 0.001$). The rate of low serum retinol (< 0.7 micromol/L) declined from 47.2% to 13.1%. In Bogandé, serum retinol increased significantly ($p < 0.001$) only in the capsule and RPO groups, going from 0.77 +/- 0.28 to 0.98 +/- 0.33 micromol/L in the former, and from 0.82 +/- 0.3 to 0.98 +/- 0.33 micromol/L in the latter. The rate of low serum retinol went from 46.1 to 17.1% in the VA capsule group and from 40.4% to 14.9% in the RPO group. VA-deficient children benefited the most from the capsule or RPO. Female sex, age and height-for-age were positively associated with the response to VA capsules or RPO. **CONCLUSION:** RPO given regularly in small amounts appears highly effective in the reduction of VA deficiency. RPO deserves more attention as a food supplement for VA and as a potential source of rural income in Sahelian countries.

Vitamin D

J Med Invest. 2006 Aug;53(3-4):204-8.

http://www.jstage.jst.go.jp/article/jmi/53/3,4/53_204/article

Impact of dietary and lifestyle on vitamin D in healthy student girls aged 11-15 years.

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OBJECTIVE: To study daily intake of calcium, phosphorus and vitamin D, to determine the biochemical findings of rickets and the effect of sunlight exposure and vitamin D supplementation in school girls with hypovitaminosis D. **METHODS:** A cross-sectional study was conducted on school girls aged 11-15 years selected randomly from various areas of Tehran, Iran. Dietary information and amount of sunlight exposure were estimated by a 7 day recalling method using self-reported questionnaire. Hypovitaminosis D defined as low serum 25-hydroxyvitamin D concentration with two or more others abnormal biochemical findings. Girls with hypovitaminosis D were randomly divided into two groups. The faces and hands of girls in group 1 were exposed to sunlight for one hour per day for twenty days, while those in group 2 were administered vitamin D capsules, 50,000 IU per day for the same period.

RESULTS: four-hundred fourteen girls evaluated, mean daily calcium intake, sunlight exposure and vitamin D requirement were 360 mg, 10 minutes and 119 IU, respectively. Mean serum 25-hydroxyvitamin D concentration was 30 ng/ml among all girls whereas in 15 (3.63%) of 414 girls was 7.8 ng/ml. Abnormal biochemical findings in these girls included hypocalcemia (n=4), hypophosphatemia (n=5), raised serum alkaline phosphatase (n=13), and parathyroid hormone (n=15). After intervention, mean serum 25-hydroxyvitamin D concentration in sunlight exposure (n=8) and vitamin D (n=7) supplementation increased to 14.4 \pm 4 ng/ml and 23 \pm 4 ng/ml respectively. There was a significant difference between the two groups (p<0.05).

CONCLUSION: Vitamin D deficiency developed in rapid growth period of girls without clear clinical rickets in sunny temperate climate city in Iran which vitamin D supplementation improved biochemical findings better than sunlight exposure.

Zinc

(See also Iron deficiency, Development)

Lancet. 2007 Mar 17;369(9565):927-34.

Effect of zinc supplementation on mortality in children aged 1-48 months: a community-based randomised placebo-controlled trial.

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BACKGROUND: Studies from Asia have suggested that zinc supplementation can reduce morbidity and mortality in children, but evidence from malarious populations in Africa has been inconsistent. Our aim was to assess the effects of zinc supplementation on overall mortality in children in Pemba, Zanzibar. **METHODS:** We enrolled 42,546 children aged 1-36 months, contributing a total of 56,507 child-years in a randomised, double-blind, placebo-controlled trial in Pemba, Zanzibar. Randomisation was by household. 21 274 children received daily supplementation with zinc 10 mg (5 mg in children younger than 12 months) for mean 484.7 days (SD 306.6). 21,272 received placebo. The primary endpoint was overall mortality, and analysis was by intention to treat. This study is registered as an International Standard Randomised Clinical Trial, number ISRCTN59549825. **FINDINGS:** Overall, there was a non-

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significant 7% (95% CI -6% to 19%; $p=0.29$) reduction in the relative risk of all-cause mortality associated with zinc supplementation. INTERPRETATION: We believe that a meta-analysis of all studies of mortality and morbidity, will help to make evidence-based recommendations for the role of zinc supplementation in public health policy to improve mortality, morbidity, growth, and development in young children.

PLoS ONE. 2007 Jun 27;2:e541.

<http://www.plosone.org/article/fetchArticle.action?articleURI=info:doi/10.1371/journal.pone.0000541>

Zinc or multiple micronutrient supplementation to reduce diarrhea and respiratory disease in South african children: a randomized controlled trial.

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BACKGROUND: Prophylactic zinc supplementation has been shown to reduce diarrhea and respiratory illness in children in many developing countries, but its efficacy in children in Africa is uncertain. **OBJECTIVE:** To determine if zinc, or zinc plus multiple micronutrients, reduces diarrhea and respiratory disease prevalence. **DESIGN:** Randomized, double-blind, controlled trial. **SETTING:** Rural community in South Africa. **PARTICIPANTS:** THREE COHORTS: 32 HIV-infected children; 154 HIV-uninfected children born to HIV-infected mothers; and 187 HIV-uninfected children born to HIV-uninfected mothers. **INTERVENTIONS:** Children received either 1250 IU of vitamin A; vitamin A and 10 mg of zinc; or vitamin A, zinc, vitamins B1, B2, B6, B12, C, D, E, and K and copper, iodine, iron, and niacin starting at 6 months and continuing to 24 months of age. Homes were visited weekly. **OUTCOME MEASURES:** Primary outcome was percentage of days of diarrhea per child by study arm within each of the three cohorts. Secondary outcomes were prevalence of upper respiratory symptoms and percentage of children who ever had pneumonia by maternal report, or confirmed by the field worker. **RESULTS:** Among HIV-uninfected children born to HIV-infected mothers, median percentage of days with diarrhea was 2.3% for 49 children allocated to vitamin A; 2.5% in 47 children allocated to receive vitamin A and zinc; and 2.2% for 46 children allocated to multiple micronutrients ($P = 0.852$). Among HIV-uninfected children born to HIV-uninfected mothers, median percentage of days of diarrhea was 2.4% in 56 children in the vitamin A group; 1.8% in 57 children in the vitamin A and zinc group; and 2.7% in 52 children in the multiple micronutrient group ($P = 0.857$). Only 32 HIV-infected children were enrolled, and there were no differences between treatment arms in the prevalence of diarrhea. The prevalence of upper respiratory symptoms or incidence of pneumonia did not differ by treatment arms in any of the cohorts. **CONCLUSION:** When compared with vitamin A alone, supplementation with zinc, or with zinc and multiple micronutrients, did not reduce diarrhea and respiratory morbidity in rural South African children. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00156832.

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J Pediatr Gastroenterol Nutr. 2007 May;44(5):619-28.

Sex-specific responses to zinc supplementation in Nouna, Burkina Faso.

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OBJECTIVES: To study the different responses by sex to zinc supplementation among young children. **STUDY CHILDREN AND METHODS:** Double-blind randomized controlled trial of zinc supplementation in 686 children aged 6-30 months, conducted in Nouna, a rural area of Burkina Faso. Children received either a 12.5-mg zinc sulfate tablet or a placebo every day for about 6 months. Outcomes were morbidity, nutritional status, and mortality. **RESULTS:** Results revealed significant differences between boys and girls in their responses to zinc supplementation. Boys who received the zinc preparation had fewer days with diarrhea than did control boys (RR = 0.88, P = 0.05), especially less nonfebrile diarrhea (RR = 0.72, P < 0.001) and less dysentery (RR = 0.65, P = 0.05), but more ear infections (RR = 4.00, P < 0.001). By contrast, girls who received the zinc supplement had the same prevalence of diarrhea as did control girls, but more dysentery (RR = 3.70, P < 0.001), fewer ear infections (RR = 0.39, P < 0.001), and fewer eye infections (RR = 0.41, P < 0.001). The effect of supplementation on nutritional status was not detectable in boys, but girls who received supplementation experienced a faster growth velocity in height than did control girls (P = 0.004) and a faster growth velocity for weight and height if they were wasted and not stunted at baseline (P = 0.003). **CONCLUSIONS:** Zinc supplementation had positive, nil, or negative effects depending on pathological condition, and the effects were different for boys than for girls. *Pediatr Infect Dis J.* 2007 Apr;26(4):306-10.

Operational feasibility of implementing community-based zinc supplementation: impact on childhood diarrheal morbidity.

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OBJECTIVE: To determine the effect of zinc supplementation on diarrheal incidence and to discover any operational constraints of zinc supplementation at the community level. **METHODS:** We included 1712 children aged between 6 and 48 months in a randomized double blind study in rural area comprising of 11 villages. Children were randomly divided into 2 groups. Zinc/placebo syrup supplementation was continued for 6 months in a weekly schedule from May 2003. Children were followed up weekly for detection of diarrhea from May 2003 until April 2004. Around 30% of the study children were evaluated every 2 months during supplementation period. **RESULTS:** During the period, 80,534 weekly visits were made giving 1548.73-child years of observation. We detected 1438 diarrheal episodes among 846 children. The incidence of diarrhea was significantly less during the supplemented period (P < 0.001; RR 0.74 (0.64-0.87)) in the zinc group. A significant difference was also noted during the follow up period (P < 0.05). In the zinc group, children <2 years of age had significantly less diarrhea during supplementation and the follow up period. Multiple episodes of diarrhea (>or=2) were significantly less in the zinc group. Approximately 85% of the surveillance workers made weekly visits to the houses and 96% of mothers administered syrup weekly to their children.

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Around 80% of mother's were aware of the possible benefits of zinc supplementation.

CONCLUSION: Weekly zinc supplementation was effective in reducing diarrheal morbidity at the community level and it was operationally feasible.

Am J Clin Nutr. 2007 Mar;85(3):887-94.

Zinc during and in convalescence from diarrhea has no demonstrable effect on subsequent morbidity and anthropometric status among infants <6 mo of age.

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BACKGROUND: Preventing illness and improving growth in the first 6 mo of life is critical to reducing infant mortality. Zinc given for 14 d at the start of diarrhea has been shown to decrease the incidence and prevalence of diarrhea and pneumonia and improve growth in the 2-3 mo after, but no trial has been done in infants <6 mo of age. **OBJECTIVE:** This study sought to assess the effect of 14 d of zinc supplementation on subsequent morbidity and growth among infants 1-5 mo of age living in Pakistan, India, and Ethiopia. **DESIGN:** Infants with acute diarrhea were randomly assigned to receive zinc (10 mg/d; n = 538) or placebo (n = 536) for 2 wk. Weekly follow-up visits were conducted for 8 wk after the diarrhea episode. Incidence and prevalence of diarrhea and prevalence of respiratory infections including pneumonia were compared between the groups. Changes in weight, length, and corresponding z scores during the 8 wk of follow-up were also compared. **RESULTS:** One thousand seventy-four infants were enrolled at the start of follow-up. The groups did not differ significantly in the proportion of infants with at least one episode of diarrhea or respiratory infections. Infants who received zinc had more days of diarrhea (rate ratio = 1.20) than did the infants who received placebo. The groups had similar prevalences of pneumonia and overall respiratory infections. No significant differences in the mean changes in weight-for-age, length-for-age, and weight-for-length z scores were observed between the groups overall or in stratified analyses. **CONCLUSION:** Young infants do not appear to benefit from 2 wk of zinc, unlike what has been observed among older children.

Comment

This study is in some contrast to one published in 2004 (Pediatrics. 2003;112:1327-32), which suggested low birth weight infants had less diarrhoea if they received zinc supplementation in the first year of life. While the response to 2 weeks of zinc after an episode of diarrhoea may not be as great in infants under 6 months as it is in older children, there may be sub-populations who will benefit.