RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

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Diarrhoea

Pediatrics. 2002 Jun;109(6):e86.

Substantial reduction in severe diarrheal morbidity by daily zinc supplementation in young north Indian children.

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OBJECTIVE: To evaluate the impact of 4 months of daily zinc supplementation on the incidence of severe and recurrent diarrhea in children 6 to 30 months of age. METHODS: A double-blind, randomized, placebo-controlled trial was conducted on children who were identified by a door-to-door survey to be aged 6 to 30 months and residing in the urban slum of Dakshinpuri, New Delhi. They were randomized to receive daily zinc gluconate (elemental zinc 10 mg to infants and 20 mg to older children) or placebo. A field attendant administered the syrup daily at home for 4 months except on Sundays, when the mother did so. One bottle that contained 250 mL was kept in the child's home and replaced monthly. Field workers visited households every seventh day during the 4-month follow-up period. At each visit, information was obtained for the previous 7 days on history of fever, number and consistency of stools, and presence of cough. When the child was ill, illness characteristics and treatment seeking outside the home were determined. If the child had diarrhea or vomiting, then dehydration was assessed. At household visits, 2 packets of oral rehydration salts were given when a child had diarrhea. Children who visited the study clinic spontaneously for illness or were referred by the field workers were treated according to the standard national program guidelines. Antibiotics were advised only for diarrhea with bloody stools or for associated illnesses. For using generalized estimating equations for longitudinal analysis of a recurring event such as diarrhea, the follow-up data for each child was divided into 17 child-periods of 7 days each and presence or absence of an incident episode of diarrhea or severe diarrhea within each 7-day period was coded. This method of analysis does not assume independence of events and therefore prevents underestimation of variance that results because of correlation of morbidity within the same child. A logistic generalized estimating equations model with exchangeable correlation covariance-variance matrix was then used to estimate the effect size. RESULTS: Zinc or placebo doses were administered on 88.8% and 91.2%, respectively, of study days during the 4 months of follow-up. There was a small but significant increase in the average number of days with vomiting in the zinc group (4.3 [standard deviation (SD): 5.8] vs 2.6 [SD 3.9] days; difference in means: 1.7 [95% confidence interval (CI): 1.3-2.1] days). At the baseline, mean plasma zinc was 62.0 microg/dL (SD: 14.3 microg/dL) in the zinc and 62.0 microg/dL (SD: 11.2 microg/dL) in the placebo group; 45.8% and 42%, respectively, had low plasma zinc levels below 60 microg/dL. At the end of the study, plasma zinc levels were substantially higher in the zinc group (ratio of geometric means: 1.94 [95% CI: 1.86-2.03]) and the proportion with low plasma zinc was lower (difference in proportions: -46.7% [95% CI: -41.8% to -51.4%]). **The incidence of diarrhea during follow-up was lower in the zinc-supplemented as compared with the placebo group (odds ratio [OR]: 0.88; 95% CI: 0.82-0.95). The beneficial impact of zinc was greater on the incidence of diarrhea with progressively increasing duration: episodes of diarrhea that lasted 1 to 6 days (OR: 0.92; 95% CI: 0.85-1.00), 7 to 13 days (OR: 0.79; 95% CI: 0.65-0.95), and > or =14 days (OR: 0.69; 95% CI: 0.48-0.98).** The impact was also greater on the incidence of episodes with progressively higher stool frequency: 3 to 5 stools per day (OR: 0.90; 95% CI: 0.83-

0.98), 6 to 9 stools per day (OR: 0.87; 95% CI: 0.77-0.98), and > or =10 per day (OR: 0.77; 95% CI: 0.63-0.94). In the zinc group, significantly more children experienced no diarrheal episode during the study period (risk ratio [RR]: 1.22; 95% CI: 1.02-1.44). Furthermore, substantially fewer children (RR: 0.51; 95% CI: 0.36-0.73) experienced recurrent diarrhea, defined as >6 diarrheal episodes in the follow-up period as compared with children in the placebo group. The number of children who were hospitalized for any cause tended to be lower in the zinc group, but the difference was not statistically significant (1.79% vs 2.43%; RR: 0.74; 95% CI: 0.43-1.27). The baseline mean plasma copper (microg/dL) was similar in the 2 groups (difference in means: 1.6; 95% CI: -2.9 to 6.1). The end study plasma copper levels were significantly lower in the zinc group (difference in means: -15.5; 95% CI: -19.9 to - 11.1). CONCLUSIONS: Zinc supplementation substantially reduced the incidence of severe and prolonged diarrhea, the 2 important determinants of diarrhea-related mortality and malnutrition. This intervention also substantially reduced the proportion of children who experienced recurrent diarrhea. Prompt measures to improve zinc status of deficient populations are warranted. The potential approaches to achieve this goal include food fortification, dietary diversification, cultivation of plants that are zinc dense or have a decreased concentration of zinc absorption inhibitors, and supplementation of selected groups of children. Future studies should assess the impact of increased zinc intakes on childhood mortality in developing countries. For facilitating intervention, there is a need to obtain reliable estimates of zinc deficiency, particularly in developing countries. The functional consequences of the effect of various doses of zinc on plasma copper levels merits additional study.

Pediatrics. 2002 May;109(5):898-903.

Effectiveness and efficacy of zinc for the treatment of acute diarrhea in young children.

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Intervention trials have shown that zinc is efficacious in treating acute diarrhea in children of developing countries. In a randomized, placebo-controlled trial, we assessed the effectiveness and efficacy of giving 3 Recommended Daily Allowances of elemental zinc to 6- to 35-month-old children with acute diarrhea. METHODS: Seventeen hundred ninety-two cases of acute diarrhea in Nepalese children were randomized to 4 study groups. Three groups were blinded and the children supplemented daily by field workers with placebo syrup, zinc syrup, or zinc syrup and a massive dose of vitamin A at enrollment. The fourth group was open and the caretaker gave the children zinc syrup daily. Day-wise information on morbidity was obtained by household visits every fifth day. RESULTS: **The relative hazards for termination of diarrhea were 26% (95% confidence interval [CI]: 8%, 46%), 21% (95% CI: 4%, 38%), and 19% (95% CI: 2%, 40%) higher in the zinc, zinc-vitamin A, and zinc-caretaker groups, respectively, than in the placebo group. The relative risks of prolonged diarrhea (duration >7 days) in these groups were 0.57 (95% CI: 0.38, 0.86), 0.53 (95% CI: 0.35, 0.81), and 0.55 (0.37, 0.84); zinc accordingly reduced the risk of prolonged diarrhea with 43% to 47%.** Five percent and 5.1% of all syrup administrations were followed by regurgitation in the zinc and zinc-vitamin A group, respectively, whereas this occurred after only 1.3% of placebo administrations. Vomiting during diarrhea was also more common in children receiving zinc. CONCLUSIONS: Three Recommended Daily Allowances of zinc given daily by caretakers or by field workers substantially reduced the duration of diarrhea. The effect of zinc was not dependent on or enhanced by concomitant vitamin A administration.

Ann Trop Paediatr. 2003 Mar;23(1):3-8.

Zinc supplementation in Brazilian children with acute diarrhoea.

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Although oral rehydration therapy greatly reduces mortality from diarrhoeal diseases, it has little effect on stool frequency. However, there is mounting evidence that zinc is an effective adjunct to the treatment of diarrhoea, although few studies have examined its efficacy in Latin America. This study assessed the efficacy of zinc supplementation in children with acute diarrhoea in Brazil. The study was a double-blind, placebo-controlled, randomised, clinical trial in children <5 years of age attending emergency services in Sergipe, Brazil. Subjects received zinc or vitamin C as placebo. **There was a marked reduction in the duration of the diarrhoea (1.1 vs 2.6 days) and of watery stools in the zinc-supplemented group.** The efficacy of zinc was independent of the presence of viral enteropathogens in the stools. It is concluded that, similar to studies in India and Bangladesh, zinc could be an important adjunct for treating acute diarrhoea in Brazilian children.

Lancet. 2002 Nov 30;360(9347):1722-7.

Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial.

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BACKGROUND: Cholera is a major public-health problem, with children most affected. However, effective single-dose antimicrobial regimens have been identified only for adults. Our aim was to compare the efficacy of azithromycin and erythromycin regimens in the treatment of children. METHODS: We did a double-blind, randomised study of 128 severely dehydrated children (age 1-15 years) with cholera, treated at one of two treatment centres in Bangladesh in 1999. Children were assigned single-dose azithromycin (20 mg/kg bodyweight, maximum individual dose 1 g; n=65) or 12.5 mg/kg erythromycin (maximum dose 500 mg; n=63) every 6 h for 3 days. Patients stayed in hospital for 5 days. We measured fluid balance every 6 h, and obtained a rectal swab or stool sample for culture daily. Our primary outcome measures were clinical success of treatment-ie, cessation of watery diarrhoea within 48 h-and bacteriological success-ie, absence of Vibrio cholerae O1 or O139 from cultures of stool or rectal swab samples after study day 2. Analysis was per protocol. FINDINGS: Two children in both groups withdrew from the study, and we excluded one child in the erythromycin group. **Treatment was clinically successful in 48 (76%) patients who received azithromycin and 39 (65%) who received erythromycin (difference 11%, 95% CI -5 to 27, p=0.244); and bacteriologically successful in 45 (71%) and 49 (82%) patients, respectively (10%, -5 to 25, p=0.261). Patients treated with azithromycin had a shorter duration of diarrhoea (median 24 h vs 42 h; difference 12 h, 0-18 h, p=0.019) and fewer episodes of vomiting (1 vs 4; difference 1 episode, 0-3 episodes, p=0.023).** INTERPRETATION: Single-dose azithromycin is as effective for treatment of cholera in children as standard erythromycin therapy, but is associated with less vomiting.

Lancet. 2002 Nov 2;360(9343):1375-80.

Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial.

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BACKGROUND: Cryptosporidiosis in children in developing countries causes persistent diarrhoea and malnutrition and is associated with increased mortality, but there is no effective treatment. We aimed to assess the effect of nitazoxanide-a new broad-spectrum antiparasitic drug-on morbidity and mortality in Zambian children with diarrhoea due to Cryptosporidium parvum. METHODS: Children with cryptosporidial diarrhoea who were admitted to the University Teaching Hospital, Lusaka, Zambia, between November, 2000, and July, 2001, and whose parents consented to their having an HIV test were randomly assigned nitazoxanide (100 mg twice daily orally for 3 days) or placebo. The primary endpoint was clinical response on day 7 after the start of treatment. Secondary endpoints included parasitological response by day 10 and mortality at day 8. Analysis was by intention to treat, with exclusion of patients subsequently found to be negative for C parvum or co-infected at baseline. The trial was stratified by HIV serology. FINDINGS: 50 HIV-seropositive and 50 HIV-seronegative children were recruited for the study, four of whom were subsequently excluded. **In HIV-seronegative children, diarrhoea resolved in 14 (56%) of 25 receiving nitazoxanide and 5 (23%) of 22 receiving placebo (difference 33%, 95% CI 7-59; p=0.037). C parvum was eradicated from stool in 13 (52%) of 25 receiving nitazoxanide and three (14%) of 22 receiving placebo (38%, 95% CI 14-63; p=0.007). Four children (18%) of 22 in the placebo group had died by day 8, compared with none of 25 in the nitazoxanide group (-18%, -34 to 2; p=0.041). HIV-seropositive children did not benefit from nitazoxanide.** Nitazoxanide was not significantly associated with adverse events in either stratum. INTERPRETATION: A 3-day course of nitazoxanide significantly improved the resolution of diarrhoea, parasitological eradication, and mortality in HIV-seronegative, but not HIV-seropositive, children.

Pediatr Infect Dis J. 2003 Aug;22(8):706-711.

Effect of oral administration of tormentil root extract (Potentilla tormentilla) on rotavirus diarrhea in children: a randomized, double blind, controlled trial.

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OBJECTIVES To determine the effectiveness of tormentil root extract (TRE) for treatment of rotavirus diarrhea in children.BACKGROUND Rotavirus, one of the most widely spread pathogens of acute, dehydrating diarrhea in children, is estimated to cause >800 000 annual deaths of young children in developing countries. Currently no rotavirus vaccine is available. Management involves rehydration therapy. Available antiperistaltic or antisecretory drugs to reduce the severity of diarrhea can cause serious side effects in children.METHODS A randomized, double blinded, placebo-controlled trial was conducted at Children's Hospital for Infectious Diseases #3, St. Petersburg, Russia in 40 children ranging in age from 3 months to 7 years with rotavirus diarrhea. We constructed 2 groups for comparison: a treatment group that consisted of 20 children treated with tormentil root extract; and a control group of 20 children who received a placebo. All patients received 3 drops of tormentil root extract or placebo per year of life, three times daily until discontinuation of diarrhea, or a maximum of 5 days. An objective method was used to evaluate diarrhea, and physical examination was used to assess degree of dehydration in children.RESULTS **The duration of diarrhea in the tormentil root extract treatment group was 3 days, compared with 5 days in the control group (P < 0.0001). In the treatment group 8 of 20 (40%) children were diarrhea-free 48 h after admission to the hospital, compared with 1 of 20 (5%) in the control group (P < 0.0001).** Subjects in the treatment group received smaller volumes of parenteral fluids than subjects in the control group.CONCLUSIONS The administration of tormentil root

extract in controlled doses shortened the duration of rotavirus diarrhea and decreased the requirement for rehydration solutions. Tormentil root extract appears to be an effective measure to treat rotavirus diarrhea in children.

Anaemia

Trop Med Int Health. 2003 Apr;8(4):310-5.

The effect on haemoglobin of the use of iron cooking pots in rural Malawian households in an area with high malaria prevalence: a randomized trial.

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BACKGROUND: Innovative low-cost sustainable strategies are required to reduce the high prevalence of iron-deficiency anaemia in developing countries. METHODS: We undertook a community-based randomized controlled intervention trial to assess the effects of cooking in iron or aluminium cooking pots in Malawian households in an area with high malaria prevalence. Analysis was by intention to treat and consistency of use. The primary outcomes were change in haemoglobin and iron status. FINDINGS: The study population comprised 164 participants eating from aluminium cooking pots and 158 from iron cooking pots. **The mean haemoglobin change was significantly increased after 6 weeks in adults who consistently ate from an iron cooking pot (+3.6 g/l compared to -3.2 g/l, mean difference between groups 6.8 g/l, 95% CI +0.86, +12.74). In children, no significant haemoglobin change was observed in consistent pot users, although they showed a significant reduction in iron deficiency (iron 8.6 ZP/g and aluminium 10.8 ZP/g, mean difference 2.2 ZP/g, 95% CI +1.08, +3.32).** INTERPRETATION: Rural Malawian adults in a high malaria transmission area who consistently consume food prepared in iron cooking pots show a significant rise in haemoglobin after 6 weeks use. Children showed a reduction in iron deficiency, but no significant improvement in haemoglobin, possibly because of their high malaria parasite prevalence. Using iron cooking pots in developing countries could provide an innovative way to prevent iron deficiency and anaemia in malarious areas where regular iron supplementation is problematic.

Interesting that the former use of iron cookware was associated with haemocromatosis, and may now be used to protect against nutritional iron deficiency. Many of the RCTs published this year are innovative strategies for the prevention or treatment of common conditions: iron cooking pots, mango supplementation instead of vitamin A capsules, getting school teachers to dispense iron.

Public Health Nutr. 2002 Jun;5(3):413-8.

A randomised trial in Mali of the effectiveness of weekly iron supplements given by teachers on the haemoglobin concentrations of schoolchildren.

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OBJECTIVE: To assess the effect on the haemoglobin concentrations of schoolchildren of

weekly iron tablets administered by teachers. DESIGN: Sixty schools were randomly assigned to two groups: in 30 schools children were given weekly for 10 weeks a tablet providing 65 mg of iron and 0.25 mg of folic acid; in the other 30 schools no iron tablets were given. All children were dewormed and given vitamin A before the study began. The haemoglobin concentration of up to 20 randomly selected children in each school was estimated before and 2 weeks after the end of treatment. SETTING: Rural community schools in Kolondieba district of Mali. SUBJECTS: Some 1113 schoolchildren aged 6-19 years with a mean of 11.4 years. RESULTS: **The haemoglobin concentration of treated children rose on average by 1.8 g l(-1) and the prevalence of anaemia fell by 8.2%; in untreated children the haemoglobin concentration fell by an average of -2.7 g l(-1) and the prevalence of anaemia rose by 9.4%. The fall in haemoglobin concentration among untreated girls of -4.0 g l(-1) was greater than in untreated boys (-0.3 g l(-1)).** CONCLUSIONS: Weekly iron tablets given by teachers prevented a general fall in the haemoglobin concentrations of untreated children, and led to a small but statistically significant rise among treated children. Young children benefited more than children aged >or=12 years, and girls benefited more than boys.

Lancet. 2002 Sep 21;360(9337):908-14.

Intermittent administration of iron and sulfadoxine-pyrimethamine to control anaemia in Kenyan children: a randomised controlled trial.

Verhoef H, West CE, Nzyuko SM, de Vogel S, van der Valk R, Wanga MA, Kuijsten A, Veenemans J, Kok FJ.

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BACKGROUND: Iron supplementation is recommended for children at high risk of anaemia, but its benefits may not outweigh the associated risk of malaria in areas of seasonal transmission. We investigated the effect on haemoglobin concentrations of intermittent administration of iron supplements and sulfadoxine-pyrimethamine in symptom-free children under intense health surveillance. METHODS: In a trial of two by two factorial design, 328 anaemic Kenyan children were randomly assigned either iron or placebo and sulfadoxine-pyrimethamine or placebo (82 to each group). Primary outcomes were haemological indicators of iron status and inflammation at the end of the follow-up, and occurrence of malaria attacks. Morbidity surveillance consisted of medical examinations every 4 weeks, continuous passive case detection, and visits twice a week to community health-workers. Analyses were by intention to treat. FINDINGS: **After 12 weeks, the groups assigned iron plus sulfadoxine-pyrimethamine, iron alone, or sulfadoxine-pyrimethamine alone had higher haemoglobin concentrations than the group assigned placebo (treatment effect adjusted for prognostic factors at baseline: 11.1 g/L [95% CI 7.5 to 14.7]; 10.7 g/L [7.1 to 14.3]; and 3.1 g/L [-0.5 to 6.7]). Administration of iron plus sulfadoxine-pyrimethamine also lowered the proportion with anaemia from 100% at baseline to 36% at 12 weeks, and of iron deficiency from 66% at baseline to 8% at 12 weeks.** Survival analysis showed no evidence of substantially increased risk of malaria after iron supplementation. INTERPRETATION: Iron supplementation gives substantial health benefits, which may outweigh possible inherent risks caused by malaria. A larger study than ours is needed to assess benefits and risks of intermittent administration of sulfadoxine-pyrimethamine in reducing the incidence of malaria attacks in areas of seasonal malaria transmission

Interesting also that this year there have been several RCTs of combined treatments to combat diseases that commonly co-exist with iron deficiency anaemia: iron deficiency and malaria, iron deficiency and Helminth infections, iron deficiency and endemic goitre.

BMJ. 2001 Dec 15;323(7326):1389-93.

Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study.

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OBJECTIVE: To measure the effects of iron supplementation and anthelmintic treatment on iron status, anaemia, growth, morbidity, and development of children aged 6-59 months. DESIGN: Double blind, placebo controlled randomised factorial trial of iron supplementation and anthelmintic treatment. SETTING: Community in Pemba Island, Zanzibar. PARTICIPANTS: 614 preschool children aged 6-59 months. MAIN OUTCOME MEASURES: Development of language and motor skills assessed by parental interview before and after treatment in age appropriate subgroups. RESULTS: Before intervention, anaemia was prevalent and severe, and geohelminth infections were prevalent and light-Plasmodium falciparum infection was nearly universal. Iron supplementation significantly improved iron status, but not haemoglobin status. **Iron supplementation improved language development by 0.8 (95% confidence interval 0.2 to 1.4) points on the 20 point scale. Iron supplementation also improved motor development, but this effect was modified by baseline haemoglobin concentrations (P=0.015 for interaction term) and was apparent only in children with baseline haemoglobin concentrations <90 g/l.** In children with a baseline haemoglobin concentration of 68 g/l (one standard deviation below the mean value), iron treatment increased scores by 1.1 (0.1 to 2.1) points on the 18 point motor scale. **Mebendazole significantly reduced the number and severity of infections caused by Ascaris lumbricoides and Trichuris trichiura, but not by hookworms. Mebendazole increased development scores by 0.4 (-0.3 to 1.1) points on the motor scale and 0.3 (-0.3 to 0.9) points on the language scale.** CONCLUSIONS: Iron supplementation improved motor and language development of preschool children in rural Africa. The effects of iron on motor development were limited to children with more severe anaemia (baseline haemoglobin concentration <90 g/l). Mebendazole had a positive effect on motor and language development, but this was not statistically significant.

Eur J Endocrinol. 2002 Dec;147(6):747-53.

Addition of microencapsulated iron to iodized salt improves the efficacy of iodine in goitrous, iron-deficient children: a randomized, double-blind, controlled trial.

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OBJECTIVE: In many developing countries, children are at high risk for both goiter and anemia. Iron (Fe) deficiency adversely effects thyroid metabolism and reduces efficacy of iodine prophylaxis in areas of endemic goiter. The study aim was to determine if co-fortification of iodized salt with Fe would improve efficacy of the iodine in goitrous children with a high prevalence of anemia. DESIGN AND METHODS: In a 9-month, randomized, double-blind trial, 6-15 year-old children (n=377) were given iodized salt (25 microg iodine/g salt) or dual-fortified salt with iodine

(25 microg iodine/g salt) and Fe (1 mg Fe/g salt, as ferrous sulfate microencapsulated with partially hydrogenated vegetable oil). RESULTS: **In the dual-fortified salt group, hemoglobin and Fe status improved significantly compared with the iodized salt group (P<0.05). At 40 weeks, the mean decrease in thyroid volume measured by ultrasound in the dual-fortified salt group (-38%) was twice that of the iodized salt group (-18%) (P<0.01). Compared with the iodized salt group, serum thyroxine was significantly increased (P<0.05) and the prevalence of hypothyroidism and goiter decreased (P<0.01) in the dual-fortified salt group.** CONCLUSION: Addition of encapsulated Fe to iodized salt improves the efficacy of iodine in goitrous children with a high prevalence of anemia.

Am J Clin Nutr. 2003 Feb;77(2):425-32.

Dual fortification of salt with iodine and microencapsulated iron: a randomized, double-blind, controlled trial in Moroccan schoolchildren.

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BACKGROUND: In many developing countries, children are at high risk of both goiter and iron deficiency anemia. OBJECTIVE: In a series of studies in northern Morocco, we developed and tested a dual-fortified salt (DFS) containing iodine and microencapsulated iron. DESIGN: To establish the DFS fortification concentration, we measured salt intake by 3-d weighed food records and estimated iron bioavailability from the local diet by using published algorithms. We then formulated a DFS containing 25 micro g iodine/g salt (as potassium iodide) and 1 mg iron/g salt (as ferrous sulfate hydrate encapsulated with partially hydrogenated vegetable oil). After storage and acceptability trials, we compared the efficacy of the DFS to that of iodized salt in a 9-mo, randomized, double-blind trial in iodine-deficient, 6-15-y-old children (n = 377). RESULTS: Mean salt intake in school-age children was 7-12 g/d, and estimated iron bioavailability from the local diet was 0.4-4.3%. After storage for 20 wk, the DFS and iodized salt were not significantly different in iodine content, and color stability was acceptable when the compounds were added to local meals. **During the efficacy trial, urinary iodine concentrations and thyroid volumes improved significantly (P < 0.001 and < 0.05, respectively) from baseline in both groups. At 40 wk, mean hemoglobin concentrations in the DFS group had increased by 14 g/L (P < 0.01), and serum ferritin, transferrin receptor, and zinc protoporphyrin concentrations were significantly better (P < 0.05) in the DFS group than in the iodized salt group. The prevalence of iron deficiency anemia in the DFS group decreased from 35% at baseline to 8% at 40 wk (P < 0.001).** CONCLUSION: A DFS containing iodine and encapsulated iron can be an effective fortification strategy.

Am J Clin Nutr. 2002 Apr;75(4):743-8.

Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Cote d'Ivoire.

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BACKGROUND: In many developing countries, children are at high risk of both goiter and iron

deficiency anemia. Iron deficiency adversely affects thyroid metabolism and may reduce the efficacy of iodine prophylaxis in areas of endemic goiter. OBJECTIVE: The aim of this study was to determine whether iron supplementation in goitrous, iron-deficient children would improve their response to iodized salt. DESIGN: We conducted a randomized, double-blind, placebo-controlled trial in 5-14-y-old children in Cote d'Ivoire. Goitrous, iron-deficient children (n = 166) consuming iodized salt (10-30 mg I/kg salt at the household level) were supplemented with either iron (60 mg Fe/d, 4 d/wk for 16 wk) or placebo. At 0, 1, 6, 12, and 20 wk, we measured hemoglobin, serum ferritin, serum transferrin receptor, whole-blood zinc protoporphyrin, thyrotropin, thyroxine, urinary iodine, and thyroid gland volume (by ultrasonography). RESULTS: Hemoglobin and iron status at 20 wk were significantly better after iron treatment than after placebo ($P < 0.05$). **At 20 wk, the mean reduction in thyroid size in the iron-treated group was nearly twice that in the placebo group (x +/- SD percentage change in thyroid volume from baseline: -22.8 +/- 10.7% compared with -12.7 +/- 10.1%; $P < 0.01$). At 20 wk, goiter prevalence was 43% in the iron-treated group compared with 62% in the placebo group ($P < 0.02$).** There were no significant differences between groups in whole-blood thyrotropin or serum thyroxine at baseline or during the intervention. CONCLUSIONS: Iron supplementation improves the efficacy of iodized salt in goitrous children with iron deficiency. A high prevalence of iron deficiency among children in areas of endemic goiter may reduce the effectiveness of iodine prophylaxis.

Int J Vitam Nutr Res. 2002 Jan;72(1):19-25.

Iron status influences the efficacy of iodine prophylaxis in goitrous children in Cote d'Ivoire.

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In the developing countries of Africa, many children are at high risk for both goiter and iron-deficiency anemia (IDA). Because iron (Fe) deficiency can have adverse effects on thyroid metabolism, Fe deficiency may influence response to supplemental iodine in areas of endemic goiter. Therefore, our aims were to determine: 1) if goitrous children also suffering from IDA could respond to oral iodine supplementation; and 2) if Fe supplementation in goitrous children with IDA would improve their response to oral iodized oil and iodized salt. First, we compared the efficacy of oral iodized oil in two groups of goitrous children: a nonanaemic group vs. an IDA group. The therapeutic response to iodized oil was impaired in the goitrous children with IDA. Second, an open trial of Fe treatment in goitrous children with IDA improved their response to oral iodized oil. Finally, in a randomized double-blind trial, goitrous, Fe-deficient children consuming iodized salt were given Fe supplementation or placebo. **Fe supplementation improved the efficacy of the iodized salt. In these studies, both anatomic (thyroid size) and biochemical (TSH, T4) measures indicated that iodine significantly improved thyroid function in the nonanaemic children compared to the Fe deficient children. Iodine was less efficacious in children with lower Hb at baseline and in those with a poorer response to Fe. The data suggest that a high prevalence of IDA among children in areas of endemic goiter may reduce the effectiveness of iodine prophylaxis.**

Epilepsy

Cochrane Database Syst Rev. 2003;(1):CD001904.

Carbamazepine versus phenobarbitone monotherapy for epilepsy.

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BACKGROUND: In developing countries, phenobarbitone is commonly used but its use in Europe and the USA has decreased due to concerns over adverse effects. Carbamazepine is recommended as the drug of choice for partial onset seizures, and there is concern that it may worsen some generalized onset seizure types. We report a review using individual patient data in which carbamazepine and phenobarbitone are compared. OBJECTIVES: To review the effects of carbamazepine compared to phenobarbitone monotherapy for people with partial onset seizures or generalized onset tonic-clonic seizures. SEARCH STRATEGY: The Cochrane Controlled trials register (Cochrane Library Issue 2, 2002); MEDLINE; EMBASE; handsearching; contacting experts and original trial investigators; contacting manufacturers of carbamazepine. SELECTION CRITERIA: Randomized or quasi-randomized, blinded or unblinded controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures. DATA COLLECTION AND ANALYSIS: Outcome measures were (i) time to withdrawal of allocated treatment, (ii) time to 12 month remission, and (iii) time to first seizure. Data were analysed using a stratified logrank analysis with results expressed as hazard ratios (HR) and 95% confidence intervals (CIs), where a HR>1 indicates an event is more likely on phenobarbitone. A test for interaction between treatment and seizure type (partial versus generalized onset) was also undertaken. MAIN RESULTS: Data are available for 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met our inclusion criteria. The main overall results (HR 95% CI) adjusted for seizure type were, (i) time to withdrawal 1.63(1.23 to 2.15), (ii) time to 12 month remission 0.87(0.65 to 1.17), (iii) time to first seizure 0.85(0.68 to 1.05). The review suggests that time to withdrawal is significantly improved with carbamazepine compared to phenobarbitone. No overall difference between drugs is identified for the outcomes 'time to 12 month remission' and 'time to first seizure'. Statistical heterogeneity was not encountered. An interaction between treatment and seizure type, confirmed statistically, was identified for time to first seizure, where phenobarbitone was favoured for partial onset seizures and carbamazepine for generalized onset tonic-clonic seizures. REVIEWER'S CONCLUSIONS: We found no overall difference between carbamazepine and phenobarbitone for time to 12 month remission or time to first seizure, however, **subgroup analyses for time to first seizure suggest an advantage with phenobarbitone for partial onset seizures and a clinical advantage with carbamazepine for generalized onset tonic-clonic seizures. Phenobarbitone is significantly more likely to be withdrawn, indicating that it is less well tolerated than carbamazepine.**

Vitamin A.

J Nutr. 2002 Dec;132(12):3693-9.

A randomized, 4-month mango and fat supplementation trial improved vitamin A status among young Gambian children.

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Supplementation with carotene-rich fruits may be an effective and sustainable approach to prevent vitamin A deficiency. To test the effectiveness of mango supplementation, 176 Gambian children, aged 2 to 7 y, were randomly assigned to one of four treatments: 75 g of dried mango containing approximately 150 micro g retinol activity equivalents with (MF) or without (M) 5 g of fat, 5 d/wk for 4 mo or 60,000 micro g of vitamin A (A) or placebo (P) capsule at baseline. After 4 mo, plasma beta-carotene was greater in both the M ($P < 0.05$) and MF ($P = 0.07$) groups compared with the P group. **After controlling for baseline plasma retinol, elevated acute phase proteins and age, plasma retinol concentrations in the A and MF, but not M, groups were higher than in the P group at the end of the study ($P < 0.01$). Increases in retinol concentrations, however, were small in both groups.** These results support the use of dietary supplementation with dried mangoes and a source of fat as one of several concurrent strategies that can be used to help maintain vitamin A status of children in developing countries where there is a severe seasonal shortage of carotenoid-rich foods.

Acta Paediatr. 2001 Oct;90(10):1107-11.

Integration of vitamin A supplementation with the Expanded Programme on Immunization: lack of impact on morbidity or infant growth.

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Vitamin A deficiency is associated with increased morbidity and mortality from diarrheal disease, measles, and malaria. It has been proposed that vitamin A supplementation could be linked with childhood immunization programs to improve child health. We conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate the impact of linking vitamin A supplementation with the Expanded Programme on Immunization on morbidity and child growth. In West Java, Indonesia, 467 six-week-old infants were randomized to receive 7.5 mg retinol equivalent (RE), 15 mg RE, or placebo with childhood immunization contacts at 6, 10, and 14 wks and 9 mo of age. Child growth was assessed through anthropometry, and morbidity histories were obtained. **Vitamin A supplementation had no apparent impact upon linear or ponderal growth or infectious disease morbidity in the first 15 mo of age when integrated with the Expanded Programme on Immunization.** CONCLUSION: Although improving vitamin A nutriture is of general importance in reducing diarrheal and measles morbidity and mortality in developing countries, this clinical trial showed no apparent benefit of vitamin A capsules for infant health when given through childhood immunization programs.

Eur J Clin Nutr. 2002 Jul;56(7):666-73.

Effects on serum retinol of multi-micronutrient supplementation and multi-helminth chemotherapy: a randomised, controlled trial in Kenyan school children.

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OBJECTIVE: To assess the effects of multi-micronutrient supplementation and multi-helminth chemotherapy on serum retinol concentration, using schools as a health delivery system. STUDY AREA AND POPULATION: From 19 primary schools in Bondo District, western Kenya, 977 children between 9 and 18 y were included in the trial. The 644 (65.9%) children on whom baseline serum retinol was available were included in this study. DESIGN: A randomised, placebo-controlled, double-blind, two-by-two factorial trial on the effects of multi-micronutrient supplementation and multi-helminth chemotherapy on serum retinol after 8 months. INTERVENTION: Single treatment with albendazole (600 mg) and praziquantel (40 mg/kg of body weight) and daily multi-micronutrient supplementation with tablet containing 1000 microg vitamin A. RESULTS: **Micronutrient supplementation (0.08 micromol/l, 95% CI 0.01, 0.14; P=0.025), but not treatment (0.03 micromol/l, 95% CI -0.04, 0.10; P=0.38), increased serum retinol.** However, treatment did increase serum retinol in S. mansoni-infected (0.09, 95% CI 0.02, 0.16; P=0.009), but not in uninfected children (-0.07, 95% CI -0.18, 0.03; P=0.18; interaction, P=0.01). Similarly, reduction in egg output of S. mansoni, but none of the geohelminth, was a predictor, corresponding to a 0.008 micromol/l (95% CI 0.00002, 0.02; P=0.049) increase in serum retinol per 100 epg reduction. Interestingly, interactions were found between age and sex (P=0.046), and malaria parasitaemia and sickle cell phenotype (P=0.04). CONCLUSION: Multi-micronutrient supplementation and reduction in S. mansoni egg output increased serum retinol, irrespective of initial serum retinol. SPONSORSHIP: The Danish International Development Assistance.

Malaria

Lancet. 2002 Oct 12;360(9340):1136-43.

Chlorproguanil-dapsone versus sulfadoxine-pyrimethamine for sequential episodes of uncomplicated falciparum malaria in Kenya and Malawi: a randomised clinical trial.

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BACKGROUND: Chlorproguanil-dapsone exerts lower resistance pressure on Plasmodium falciparum than does sulfadoxine-pyrimethamine, but is rapidly eliminated. We aimed to find out whether chlorproguanil-dapsone results in a higher retreatment rate for malaria than sulfadoxine-pyrimethamine. METHODS: In a randomised trial of paediatric outpatients with uncomplicated falciparum malaria, patients received either chlorproguanil-dapsone or sulfadoxine-pyrimethamine and were followed up for up to 1 year. Sites were in Kenya (n=410) and Malawi (n=500). We used per-protocol analysis to assess the primary outcome of annual malaria incidence. FINDINGS: Drop-outs were 117 of 410 (28.5%) in Kenya, and 342 of 500 (68.4%) in Malawi. Follow-up was for a median of 338 days (IQR 128-360) and 342 days (152-359) in Kilifi (chlorproguanil-dapsone and sulfadoxine-pyrimethamine, respectively), and for 120 days (33-281) and 84 days (26-224) in Blantyre. **Mean annual malaria incidence was 2.5 versus 2.1 in Kenya (relative risk 1.16, 95% CI 0.98-1.37), and 2.2 versus 2.8 in Malawi (0.77, 0.63-0.94). 4.3% versus 12.8%, and 5.4% versus 20.1%, of patients were withdrawn for treatment failure in Kenya and Malawi, respectively.** In Kenya haemoglobin concentration of 50 g/L or less caused exit in 6.9% of chlorproguanil-dapsone patients and 1.5% of sulfadoxine-pyrimethamine patients, but most anaemia occurred before re-treatment. In Malawi only one patient exited because of anaemia. INTERPRETATION: Despite the rapid elimination of chlorproguanil-dapsone, children treated with this drug did not have a higher incidence of malaria episodes than those treated with

sulfadoxine-pyrimethamine. Treatment failure was more common with sulfadoxine-pyrimethamine. Cause of anaemia in Kenya was probably not adverse reaction to chlorproguanil-dapsone, but this observation requires further study.

Lancet. 2002 Dec 21-28;360(9350):2031-8.

Sulfadoxine/pyrimethamine alone or with amodiaquine or artesunate for treatment of uncomplicated malaria: a longitudinal randomised trial.

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BACKGROUND: New antimalarial treatments are urgently needed in sub-Saharan Africa. Improved therapies should decrease failure rates in the short term, but their effect on incidence of subsequent episodes of malaria is little studied. We aimed to compare the short-term and long-term effectiveness of three antimalarial regimens in children from Kampala, Uganda. METHODS: We randomly allocated healthy children aged 6 months to 5 years to receive 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine plus either placebo, 25 mg/kg amodiaquine, or 12 mg/kg artesunate. Participants were followed up for 1 year and received the same preassigned treatment for every new episode of uncomplicated malaria diagnosed during follow-up. Recrudescent and new infections were distinguished by comparison of polymorphisms in merozoite surface protein 2 (MSP2). Our primary endpoint was the total number of treatments for malaria per time at risk. Analyses were done per protocol. FINDINGS: 183 (61%) of 316 participants were diagnosed with at least one episode of uncomplicated malaria. A total of 577 episodes of uncomplicated Plasmodium falciparum malaria were treated with study drugs; all regimens were safe and well tolerated. **Clinical treatment failure after 14 days was significantly more frequent in the sulfadoxine/pyrimethamine group (38 of 215, 18%) compared with either the sulfadoxine/pyrimethamine plus amodiaquine group (two of 164, 1%; p<0.0001) or sulfadoxine/pyrimethamine plus artesunate group (one of 198, 1%; p<0.0001). After 28 and 42 days, patients in the sulfadoxine/pyrimethamine plus amodiaquine group were significantly less likely to develop malaria than were those in the other groups. Overall, sulfadoxine/pyrimethamine plus amodiaquine reduced the rate of subsequent treatments for malaria by 54% (95% CI 36-66, p<0.0001) compared with sulfadoxine/ pyrimethamine alone and by 37% (12-54, p=0.007) compared with sulfadoxine/pyrimethamine plus artesunate.** INTERPRETATION: Sulfadoxine/pyrimethamine plus amodiaquine could be used as an inexpensive regimen to decrease the rate of subsequent episodes of malaria.

Lancet. 2002 Apr 20;359(9315):1365-72.

Amodiaquine-artesunate versus amodiaquine for uncomplicated Plasmodium falciparum malaria in African children: a randomised, multicentre trial.

Adjuik M, Agnamey P, Babiker A, Borrmann S, Brasseur P, Cisse M, Cobelens F, Diallo S, Faucher JF, Garner P, Gikunda S, Kremsner PG, Krishna S, Lell B, Loolpapit M, Matsiegui PB, Missinou MA, Mwanza J, Ntoumi F, Olliaro P, Osimbo P, Rezbach P, Some E, Taylor WR.

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BACKGROUND: Increasing drug resistance limits the choice of efficacious chemotherapy against

Plasmodium falciparum malaria in Africa. Amodiaquine still retains efficacy against P falciparum in many African countries. We assessed the safety, treatment efficacy, and effect on gametocyte carriage of adding artesunate to amodiaquine in three randomised trials in Kenya, Senegal, and Gabon. METHODS: We enrolled 941 children (400 in Kenya, 321 in Senegal, and 220 in Gabon) who were 10 years or older and who had uncomplicated P falciparum malaria. Patients were randomly assigned amodiaquine (10 mg/kg per day for 3 days) plus artesunate (4 mg/kg per day for 3 days) or amodiaquine (as above) and placebo (for 3 days). The primary endpoints were parasitological cure rates at days 14 and 28. Analysis was by intention to treat and by an evaluability method. FINDINGS: Both regimens were well tolerated. Six patients in the amodiaquine-artesunate group and five in the amodiaquine group developed early, drug-induced vomiting, necessitating alternative treatment. **By intention-to-treat analysis, the day-14 cure rates for amodiaquine-artesunate versus amodiaquine were: 175/192 (91%) versus 140/188 (74%) in Kenya (D=16.7% [95% CI 9.3-24.1], p<0.0001), 148/160 (93%) versus 147/157 (94%) in Senegal (-1.1% [-6.7 to 4.5], p=0.7), and 92/94 (98%) versus 86/96 (90%) in Gabon (8.3% [1.5-15.1], p=0.02). The corresponding rates for day 28 were: 123/180 (68%) versus 75/183 (41%) in Kenya (27.3% [17.5-37.2], p<0.0001), 130/159 (82%) versus 123/156 (79%) in Senegal (2.9% [-5.9 to 11.7], p=0.5), and 80/94 (85%) versus 70/98 (71%) in Gabon (13.7% [2.2-25.2], p=0.02).** Similar rates were obtained by evaluability analysis. INTERPRETATION: The combination of artesunate and amodiaquine improved treatment efficacy in Gabon and Kenya, and was equivalent in Senegal. Amodiaquine-artesunate is a potential combination for use in Africa. Further investigations to assess the potential effect on the evolution of drug resistance, disease transmission, and safety of amodiaquine-artesunate are warranted.

Meningitis

Ann Trop Paediatr. 2002 Jun;22(2):145-57.

Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial.

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A multi-centre randomised open trial was done to determine whether moderate oral fluid restriction or intravenous fluid at full maintenance volumes would result in a better outcome for children with bacterial meningitis in Papua New Guinea, and what clinical signs could guide fluid management. Children with clinical signs and cerebrospinal fluid suggestive of bacterial meningitis received either breast milk by nasogastric tube at 60% of normal maintenance volumes (n = 172) or intravenous half-normal saline and 5% dextrose at 100% of normal maintenance volumes (n = 174) for the 1st 48 hrs of treatment. An adverse outcome was death or severe neurological sequelae, and a good outcome was defined as intact survival or survival with at worst mild-to-moderate neurological sequelae. **The probability of an adverse outcome was 24.7% in the intravenous group and 33.1% in the oral-restricted group, but the difference was not statistically significant (RR 0.75, 0.53-1.04, p = 0.08). Sunken eyes or reduced skin turgor at presentation were risk factors for an adverse outcome (OR 5.70, 95% CI 2.87-11.29) and were most strongly associated with adverse outcome in the fluid-restricted group. Eyelid oedema during treatment was also a risk factor for an adverse outcome (OR 2.54, 95% CI 1.36-4.75) and eyelid oedema was much more common in the intravenous group (26%) than in the restricted group (5%).** For many children with bacterial meningitis in less developed countries, moderate fluid restriction is unnecessary and will be harmful; a normal state of hydration should be achieved

but over-hydration should be avoided. Giving 100% of normal maintenance fluids, especially with intravenous hypotonic fluid, will lead to oedema in up to one quarter of children with bacterial meningitis. If additional intravenous fluids are required for children with meningitis, an isotonic solution should be used.

Lancet. 2002 Jul 20;360(9328):211-8.

Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial.

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BACKGROUND: Steroids are used as adjuvant treatment in childhood pyogenic meningitis to attenuate host inflammatory responses to bacterial invasion. We aimed to assess the effectiveness of dexamethasone in management of acute bacterial meningitis in a developing country. METHODS: In a double-blind, placebo controlled trial, we included 598 children with pyogenic meningitis who had been admitted to the children's wards of the Queen Elizabeth Central Hospital, Blantyre, Malawi. We did physical, neurological, developmental, and hearing assessments at 1 and 6 months after discharge. The primary outcome was overall death. Secondary outcomes included sequelae, in-hospital deaths, and death after discharge. Analysis was done by intention to treat. FINDINGS: Of the 598 included children, 307 (51%) were assigned to dexamethasone and 295 (49%) to placebo. 338 (40%) of 598 patients had Streptococcus pneumoniae, 170 (28%) Haemophilus influenzae type b, 66 (11%) Neisseria meningitidis, and 29 (5%) Salmonella spp. 78 (13%) patients had no growth on culture. **The number of overall deaths was the same in the two treatment groups (relative risk 1.00 [95% CI 0.8-1.25], p=0.93). At final outcome, sequelae were identified in 84 (28%) of children on steroids and in 81 (28%) on placebo (relative risk 0.99 [95% CI 0.78-1.27], p=0.97). The number of children dying in hospital did not differ between groups.** INTERPRETATION: Steroids are not an effective adjuvant treatment in children with acute bacterial meningitis in developing countries.

Acute respiratory infection vaccines and treatment

Pediatr Infect Dis J. 2002 Feb;21(2):138-41.

Haemophilus influenzae type b conjugate vaccine diluted tenfold in diphtheria-tetanus-whole cell pertussis vaccine: a randomized trial.

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BACKGROUND: Despite their proven efficacy Haemophilus influenzae type b (Hib) conjugate vaccines are not given to most children in the developing world in the face of an estimated global Hib disease burden of nearly 2 million cases per annum. A major barrier to the introduction of the vaccine would be overcome by diluting the vaccine 10-fold in diphtheria-tetanus-whole cell pertussis (DTP). We report a randomized trial comparing the use of Hib conjugate vaccine diluted in a multidose vial of DTP with that of the full Hib dose. METHODS: We randomized 168 infants

to receive either the full dose Hib polysaccharide-tetanus toxoid conjugate (PRP-T) vaccine or a 1/10 dilution prepared by reconstituting the full dose in a 10-dose DTP vial. Infants were vaccinated at 6, 10 and 14 weeks of age and received a full dose as a test of immunologic memory at 9 months of age. Sera were collected at each visit and at 1 week after the booster dose. Serum anti-capsular PRP antibody concentrations were measured by enzyme-linked immunosorbent assay. RESULTS: After the primary vaccination series, **95% of infants in the full dose arm and 94% of infants in the 1/10 dose arm achieved anti-PRP IgG antibody concentrations of > or = 1.0 microg/ml. Infants receiving the diluted vaccine had significantly higher titers of anti-PRP antibody in response to the booster dose (151.36 microg/ml vs. 68.55 microg/ml, P = 0.009).** CONCLUSIONS: The 1/10 dose of PRP-T was as immunogenic and safe as the full dose. The technique of diluting a single dose of PRP-T in a 10-dose DTP vial could potentially allow the widespread introduction of Hib vaccine in resource-poor countries currently unable to afford full dose Hib conjugate vaccine.

BMJ. 2002 Jun 8;324(7350):1358.

Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum.

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OBJECTIVES: To evaluate the effect of daily zinc supplementation in children on the incidence of acute lower respiratory tract infections and pneumonia. DESIGN: Double masked, randomised placebo controlled trial. SETTING: A slum community in New Delhi, India. PARTICIPANTS: 2482 children aged 6 to 30 months. INTERVENTIONS: Daily elemental zinc, 10 mg to infants and 20 mg to older children or placebo for four months. Both groups received single massive dose of vitamin A (100 000 IU for infants and 200 000 IU for older children) at enrollment. MAIN OUTCOME MEASURES: All households were visited weekly. Any children with cough and lower chest indrawing or respiratory rate 5 breaths per minute less than the World Health Organization criteria for fast breathing were brought to study physicians. RESULTS: At four months the mean plasma zinc concentration was higher in the zinc group (19.8 (SD 10.1) v 9.3 (2.1) micromol/l, P<0.001). **The proportion of children who had acute lower respiratory tract infection during follow up was no different in the two groups (absolute risk reduction -0.2%, 95% confidence interval -3.9% to 3.6%). Zinc supplementation resulted in a lower incidence of pneumonia than placebo (absolute risk reduction 2.5%, 95% confidence interval 0.4% to 4.6%). After correction for multiple episodes in the same child by generalised estimating equations analysis the odds ratio was 0.74, 95% confidence interval 0.56 to 0.99.** CONCLUSIONS: Zinc supplementation substantially reduced the incidence of pneumonia in children who had received vitamin A.

Arch Dis Child. 2002 Feb;86(2):113-8.

Clinical efficacy of co-trimoxazole versus amoxicillin twice daily for treatment of pneumonia: a randomised controlled clinical trial in Pakistan.

Catchup Study Group.

AIMS: To compare the clinical efficacy of twice daily oral co-trimoxazole with twice daily oral amoxicillin for treatment of childhood pneumonia. METHODS: Randomised controlled, double blind, multicentre study in outpatient departments of seven hospitals and in one community health

service. A total of 1471 children (aged 2-59 months) with non-severe pneumonia were randomly assigned to 25 mg/kg amoxicillin (n = 730) or 4 mg/kg trimethoprim plus 20 mg/kg sulphamethoxazole (co-trimoxazole) (n = 741). Both medicines were given orally twice daily for five days. RESULTS: Data from 1459 children were analysed: 725 were randomised to amoxicillin and 734 to co-trimoxazole. **Treatment failure in the amoxicillin group was 16.1% compared to 18.9% in the co-trimoxazole group.** Multivariate analysis showed that treatment failure was more likely in infants who had history of difficult breathing or those who had been ill for more than three days before presentation. CONCLUSIONS: Both amoxicillin and co-trimoxazole were equally effective in non-severe pneumonia. Good follow up of patients is essential to prevent worsening of illness.

Lancet. 2002 Feb 9;359(9305):474-80.

Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial.

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BACKGROUND: Pneumonia is the most frequent cause of child mortality in less-developed countries. We aimed to establish whether the combination of benzylpenicillin and gentamicin or chloramphenicol would be better as first-line treatment in children with severe pneumonia in Papua New Guinea. METHODS: We did an open randomised trial in which we enrolled children aged 1 month to 5 years of age who fulfilled the WHO criteria for very severe pneumonia and who presented to hospitals in two provinces. Children were randomly assigned to receive chloramphenicol (25 mg/kg 6 hourly) or benzylpenicillin (50 mg/kg 6 hourly) plus gentamicin (7.5 mg/kg daily) by intramuscular injection. The primary outcome measure was a good or an adverse outcome. FINDINGS: 1116 children were enrolled; 559 children were treated with chloramphenicol and 557 with benzylpenicillin and gentamicin. At presentation the median haemoglobin oxygen saturation was 71% (IQR 57-77) for those allocated chloramphenicol and 69% (55-77) for those allocated penicillin and gentamicin. **147 (26%) children treated with chloramphenicol and 123 (22%) treated with penicillin and gentamicin had adverse outcomes (p=0.11). 36 children treated with chloramphenicol and 29 treated with penicillin and gentamicin died.** More children treated with chloramphenicol than penicillin and gentamicin represented with severe pneumonia within 1 month of hospital discharge (p=0.03). INTERPRETATION: For children with severe pneumonia in less-developed countries the probability of a good outcome is similar if treated with chloramphenicol or with the combination of benzylpenicillin and gentamicin.

Tuberculosis

Control Clin Trials. 2002 Oct;23(5):540-53.

Design of the Brazilian BCG-REVAC trial against tuberculosis: a large, simple randomized community trial to evaluate the impact on tuberculosis of BCG revaccination at school age.

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This paper describes the design and baseline results of a large and simple randomized controlled trial of the protection against tuberculosis of a dose of Bacillus Calmette Guerin (BCG) vaccination given to school children in a population with a high coverage of neonatal BCG (The Brazilian BCG-REVAC trial). The study started in 1996 and is a pair-matched and stratified-cluster randomized controlled trial with no placebo. The study population consists of children aged 7-14 years enrolled in 763 state schools from the cities of Salvador and Manaus, Brazil. Schools were the unit of randomization. Identifying information was collected for 354,708 school children. The final study population, after exclusions on the basis of age, BCG scar readings and absence from school on the day of the study visit, consists of 242,401 children, of whom 125,403 are in intervention schools. Follow-up relies on ascertainment of cases diagnosed at the health services and notified to the tuberculosis control program surveillance system. Blindness is guaranteed during linkage and validation of cases. Analysis is planned for the next 12 months, where efficacy will be estimated by calculating incidence of tuberculosis in the vaccine and control groups, taking into consideration the cluster design. The intervention studied, a second BCG vaccination, is widely used, although the World Health Organization does not recommend it on the basis of absence of evidence of protection or lack of protection. The results of the trial will make it possible for BCG revaccination practice to be informed by evidence. This is an example of a large simple and relatively inexpensive effectiveness trial, resulting from good collaboration between academia and health and education services enabling developing countries to define policies that are relevant for their reality.

Skin disease and headlice

J Paediatr Child Health. 2002 Aug;38(4):401-4.

Ivermectin is better than benzyl benzoate for childhood scabies in developing countries.

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OBJECTIVE: To compare single dose oral ivermectin with topical benzyl benzoate for the treatment of paediatric scabies. METHODS: An observer-blinded randomized controlled trial was undertaken at Vila Central Hospital, Vanuatu. One hundred and ten children aged from 6 months to 14 years were randomized to receive either ivermectin 200 micro g/kg orally or 10% benzyl benzoate topically. Follow up was at 3 weeks post-treatment. Primary outcome measures were the number of scabies lesions, the itch visual analogue score and nocturnal itch. Secondary outcome measures were the skin's reaction to treatment, the passage of worms in stool and other side effects. RESULTS: Eighty patients completed the study protocol. **There was no significant difference between the two treatments; both produced a significant decrease in the number of scabies lesions seen at follow up. Ivermectin cured 24 out of 43 patients (56%), and benzyl benzoate 19 out of 37 patients (51%) at 3 weeks post-treatment. No serious side effects were noted with either treatment, but benzyl benzoate was more likely to produce local skin reactions (P = 0.004, OR 6.4, 95% CI 1.6-25.0)** CONCLUSIONS: Ivermectin is cheap and effective in the treatment of paediatric scabies. Ivermectin has minimal observed toxicity and has the additional beneficial effects of antiparasitic action in onchocerciasis, filariasis and strongyloidiasis. Ivermectin is better than benzyl benzoate for the treatment of paediatric scabies in developing countries.

Cochrane Database Syst Rev. 2001;(3):CD001165.

Interventions for treating headlice.

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BACKGROUND: Infection with head lice is a widespread condition in developed and developing countries. Infection occurs most commonly in children, but also affects adults. If left untreated the condition can become intensely irritating and skin infections may occur if the bites are scratched. OBJECTIVES: The aim of this review was to assess the effects of interventions for head lice. SEARCH STRATEGY: Trials register of The Cochrane Infectious Diseases Group; Medline; Embase; Science Citation Index; Biosis and Toxline; reference lists of relevant articles; pharmaceutical companies producing pediculicides (published and unpublished trials); UK and US Regulatory Authorities. SELECTION CRITERIA: Randomised trials (published and unpublished) or trials using alternate allocation were sought which compared pediculicides with the same and different formulations of other pediculicides, and pediculicides with physical methods. DATA COLLECTION AND ANALYSIS: Of the 71 identified studies, only four met the inclusion criteria. Two reviewers independently assessed trial quality. One reviewer extracted the data. MAIN RESULTS: **We found no evidence that any one pediculicide has greater effect than another.** The two studies comparing malathion and permethrin with their respective vehicles showed a higher cure rate for the active ingredient than the vehicle. Another study comparing synergised pyrethrins with permethrin showed their effects to be equivalent. A comparative trial of malathion lotion vs combing, showed combing to be ineffective for the cureative treatment of head lice infection. Adverse effects were reported in a number of trials and were all minor, although reporting quality varied between trials. REVIEWER'S CONCLUSIONS: Permethrin, synergised pyrethrin and malathion were effective in the treatment of head lice. However, the emergence of drug resistance since these trials were conducted means there is no direct contemporary evidence of the comparative effectiveness of these products. The 'best' choice will now depend on local resistance patterns. Physical treatment methods(BugBusting) were shown ot be ineffective to treat head lice. No evidence exists regarding other chemical control methods such as the use of herbal treatments, when used in the curative treatment of head lice. Future trials should take into account the methodological recommendations that arise from this review.

Leishmaniasis

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Insecticide impregnated curtains to control domestic transmission of cutaneous leishmaniasis in Venezuela: cluster randomised trial.

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OBJECTIVE: To measure the impact on transmission of leishmaniasis of curtains impregnated with insecticide. DESIGN: Cluster randomised controlled trial: household interview survey,

observational study of people's behaviour, entomological study with light trap captures of sandflies inside houses. SETTING: 14 urban sectors in Trujillo, Venezuela. PARTICIPANTS: 2913 inhabitants of 569 houses. INTERVENTION: Sectors were paired according to their 12 month cumulative incidence of cutaneous leishmaniasis, one sector in each pair was randomly allocated to receive polyester curtains impregnated with lambdacyhalothrin (intervention group) while the other sector received curtains without insecticide or no curtains (control groups). After 12 months a follow up household survey was conducted. MAIN OUTCOME MEASURES: Reduction in abundance of sandflies indoors and 12 month incidence of clinical cases of cutaneous leishmaniasis. RESULTS: Transmission of cutaneous leishmaniasis occurred mainly in the domestic setting, with the incidence over 12 months of 4%. The mean number of sandflies per trap per night was 16. **After follow up the 12 month incidence of cutaneous leishmaniasis was 0% in the intervention group and 8% in the six pairs in the control group that received unimpregnated curtains (mean difference 8, 95% confidence interval 4.22 to 11.78; P=0.001). There were significantly fewer sandflies in the intervention group (2 v 15, mean difference 13 sandflies per trap; 9 to 17; P<0.001).** CONCLUSION: Curtains impregnated with insecticide provide a high degree of protection against indoor transmission of cutaneous leishmaniasis.

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Effect of insecticide-impregnated dog collars on incidence of zoonotic visceral leishmaniasis in Iranian children: a matched-cluster randomised trial.

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BACKGROUND: Deltamethrin-impregnated dog collars reduce sandfly bite rates on dogs, and are effective in killing sandflies that attempt to feed. Because domestic dogs are the principal reservoir hosts of zoonotic visceral leishmaniasis, we tested whether community-wide application of dog collars could protect children against infection with Leishmania infantum, the parasite that causes the disease. METHODS: 18 villages were paired, matched by preintervention child prevalence of L infantum infection. Within pairs, villages were randomly assigned to either control or intervention. All domestic dogs in intervention villages were provided with collars for the transmission season. The main outcome measure was incidence of L infantum infection after 1 year measured by seroconversion. Secondary outcomes were leishmanin skin test (LST) conversion and seroconversion in dogs. FINDINGS: **The seroconversion rate in children was 1.49% (17/1141) in the intervention villages and 2.41% (26/1078) in control villages (odds ratio 0.57, 95% CI 0.36-0.90, p=0.017).** LST conversion was also lowered, but not significantly (odds ratio 0.66, 0.41-1.08, p=0.096). The seroconversion rate in dogs in intervention villages was also significantly reduced (0.46, 0.30-0.70, p=0.0003). INTERPRETATION: Community-wide application of deltamethrin-impregnated dog collars not only protects domestic dogs from L infantum infections, but might also reduce the risk of L infantum infection in children. These dog collars could have a role in control of visceral leishmaniasis and replace controversial dog culling programmes in some countries. However, the effectiveness of dog collars will depend on the importance of wild versus domestic canids as reservoir hosts of L infantum.