RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

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SEARCH STRATEGY

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Iron Deficiency

Comment

Supplemental iron probably doesn't substantially increase the risk of malaria in children with sickle cell trait, although the power of this study below was quite low (and the confidence intervals broad), so only a large effect is excluded. When giving iron it is valuable to also provide advice about iron rich foods and other nutritional education to mothers. Iron supplementation given daily is probably more effective in increasing the Hb than iron given twice weekly. Giving mebendazole every 3 months reduces anaemia and wasting malnutrition in children less than 3 years (but may increase the risk of atopy in populations with high rates of helminth infections)

Am J Clin Nutr. 2004 Mar;79(3):466-72.

Relation between the response to iron supplementation and sickle cell hemoglobin phenotype in preschool children in western Kenya.

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BACKGROUND: Iron supplementation has been associated with greater susceptibility to malaria and lower hematologic responses in pregnant Gambian women with sickle cell trait (HbAS) than in similar women with the normal (HbAA) phenotype. It is not known whether a similar interaction exists in children. OBJECTIVE: Our aim was to determine the influence of the HbAS phenotype on hematologic responses and malaria after iron supplementation in anemic (hemoglobin: 70-109 g/L) children aged 2-35 mo. DESIGN: We conducted a double-blind, randomized, placebo-controlled trial (HbAS, n = 115; HbAA, n = 408) of intermittent preventive treatment with sulfadoxine pyrimethamine (IPT-SP) at 4 and 8 wk and daily supervised iron for 12 wk. RESULTS: **The mean difference in hemoglobin concentrations at 12 wk between children assigned iron and placebo iron, after adjustment for the effect of IPT-SP, was 9.1 g/L (95% CI: 6.4, 11.8) and 8.2 g/L (4.0, 12.4) in HbAA and HbAS children, respectively (P for interaction = 0.68). Although malaria parasitemia and clinical malaria occurred more often in HbAS children in the iron group than in those in the placebo iron group, this difference was not significant; incidence rate ratios were 1.23 (95% CI: 0.64, 2.34) and 1.41 (0.39, 5.00), respectively.** The corresponding incidence rate ratios in HbAA children in the same groups were 1.07 (95% CI: 0.77, 1.48) and 0.59 (0.35, 1.01), respectively. The corresponding interactions between the effects of iron and hemoglobin phenotype were not significant. CONCLUSIONS: There was no evidence for a clinically relevant modification by the hemoglobin S phenotype of the effects of iron supplementation in the treatment of mild anemia. **The benefits of iron supplementation are likely to outweigh possible risks associated with malaria in children with the HbAA or HbAS phenotype.**

Indian Pediatr. 2003 Dec;40(12):1131-44.

Effectiveness of nutrition education, iron supplementation or both on iron status in children.

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OBJECTIVE: A community-based, randomized trial was designed to **compare the effect of nutrition education and/or iron supplementation (weekly) on iron status of children in an urban slum in Delhi**. METHODS: Four hundred and fifty one children, 9-36 months of age and their caretakers (mothers), assigned to one of the following groups were included in the cohort. Group 1, nutrition education. Group 2, supplementation (with 20 mg elemental iron). Group 3, nutrition education with supplementation (with 20 mg elemental iron) and Group 4, control given placebo. The intervention program was of four months duration, with a treatment phase of 8 wk followed by 8 wk of no treatment. RESULTS: **Post intervention, at 8 wk and at 16 wk, the hemoglobin change in the nutrition education, supplementation, nutrition education with supplementation and control groups was 2.9, 1.9, 3.8 and -5.9%, respectively and 2.1, -1.9, 0 and -9.3%, respectively (as compared to initial values).** There was no significant effect of any of the intervention at 8 weeks. At 16 wk, there was significant positive effect of nutrition education group (p less than 0.05). The percent change in serum ferritin value at 16 wk in the nutrition education, supplementation, nutrition education with supplementation and control groups was 5.7, -2.3, -3.4 and -40%, respectively. **Serum ferritin values were significantly higher for the nutrition education group ($p < 0.001$) as compared to the control. At 16 wk, the nutrition education group mothers showed significantly higher nutrition knowledge and the dietary iron intake of children was significantly higher than their control group counterparts ($p < 0.0001$).** CONCLUSION: The study suggests that nutrition education did have a positive effect on the iron status possibly by improving the dietary iron intake.

Trans R Soc Trop Med Hyg. 2004 Apr;98(4):218-27.

Effects of iron and multimicronutrient supplementation on geophagy: a two-by-two factorial study among Zambian schoolchildren in Lusaka.

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Geophagy has been associated with iron deficiency and anaemia, but no causal relationship has been established. To clarify this, we conducted a two-by-two factorial randomised, controlled trial on the effect of iron and multimicronutrient supplementation on geophagy in Zambian schoolchildren in Lusaka, from February to December 2001. Of the 406 children, 212 (52.2%) were girls and the mean (range) age was 10.2 (7-15) years. Geophagy was reported by 302 (74.4%) and more often in girls than in boys (80.2 vs. 67.7%, P = 0.007). The mean (range)

daily earth intake was 25.2 (1-200) g. Geophageous children had more often geophageous relatives than non-geophageous children (79.5 vs. 1.9%, P < 0.001). Geophageous children had lower serum ferritin (20.5 vs. 25.0 microg/l, P = 0.032) but not haemoglobin (Hb) (129.2 vs. 130.4 g/l, P = 0.59), than non-geophageous. Among those with Hb < 130 g/l, geophageous children had significantly higher prevalence (53.7 vs. 30.6%, P = 0.024) of Ascaris lumbricoides infection than non-geophageous. The prevalence of geophagy (74.4 to 51.6%) and the intake of earth (25.3 to 15.0 g/day) declined (P = 0.001 and P < 0.001, respectively) among the 220 (54.2%) children followed-up. In bivariate analysis, non-iron supplementation reduced the prevalence of geophagy more than iron supplementation did, but this was not confirmed in the multiple logistic regression analysis. Multimicronutrients had no effect on either geophagy prevalence or earth intake. **Geophagy was prevalent and associated with iron deficiency, but iron supplementation had no effects on geophageous behaviour. Geophagy could be a copied behaviour and the association between geophagy and iron deficiency due to impaired iron absorption following earth eating.**

J Nutr. 2004 May;134(5):1167-74.

Daily iron supplementation is more efficacious than twice weekly iron supplementation for the treatment of childhood anemia in western Kenya.

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A recent meta-analysis of 14 clinical trials indicated that daily compared with intermittent iron supplementation resulted in significantly greater hematological improvement in pregnant women. No such definitive beneficial effect was demonstrated in preschool children. We compared the efficacy of daily and twice weekly iron supplementation for 6 wk under supervised and unsupervised conditions in the treatment of mild and moderate anemia [hemoglobin (Hb) 50-109 g/L] in children aged 2-59 mo living in a malaria-endemic area of western Kenya. The study was a cluster-randomized trial using a factorial design; participants were aware of the treatment assigned. All children (n = 1049) were administered a single dose of sulfadoxine-pyrimethamine at enrollment followed by 6 wk of daily supervised iron supplementation [3-6 mg/(kg.d)], twice weekly supervised iron supplementation [6-12 mg/(kg.wk)], daily unsupervised iron supplementation, or twice weekly unsupervised iron supplementation. **In the supervised groups, Hb concentrations at 6 and 12 wk (6 wk postsupplementation) were significantly higher in children given iron daily rather than twice weekly [mean (95% CI) difference at 6-wk: 4.2 g/L (2.1, 6.4); 12-wk: 4.4 g/L (1.8, 7.0)]. Among the unsupervised groups, Hb concentrations were not different at 6 wk [mean (95% CI) difference: 0.86 g/L (-1.4, 3.1)], but significantly higher at 12 wk for those assigned daily iron [mean (95% CI) difference: 3.4 g/L (0.79, 6.0), P = 0.02]. In this malarious area and after initial antimalarial treatment, 6 wk of daily iron supplementation results in better hematological responses than twice weekly iron supplementation in the treatment of anemia in preschool children, regardless of whether adherence can be ensured.**

Pediatr Hematol Oncol. 2003 Jun;20(4):319-26.

Effect of twice weekly versus daily iron treatment in Turkish children with iron deficiency anemia.

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This study was designed to propose a more practical, effective, safer, inexpensive, and manageable alternative treatment of iron deficiency anemia (IDA) for the developing countries. The study involves 94 children between the ages of 5 months and 6 years who had been seen in the authors' hospital and diagnosed as having iron deficiency anemia. Ninety-four children with IDA were randomly divided into two groups: **48 children comprised the first group, which was administered conventional treatment, and 46 children comprised the second group, which was administered intermittent treatment involving iron administration 2 days a week.** Twenty-three children whose age and gender distribution were compatible with the other groups were included in the study as the control group. Both groups were reevaluated for their initial hematologic parameters at the end of the treatment. **When the parameters of both groups were compared with the parameters of the control group after the treatment, there were no differences between hemoglobin, hematocrit, red blood cell, mean corpuscular volume, mean corpuscular hemoglobin concentration, serum iron, and ferritin levels of conventional and intermittent treatment groups. With respect to certain parameters, such as red cell distribution, serum iron binding capacity, transferrin saturation, transferrin receptor, and transferrin receptor/log ferritin, however, intermittent treatment was superior to the conventional treatment method (p <.05).** In IDA, when a conventional treatment method or an intermittent treatment method is used, there are no differences between the hematological parameters. In fact, the intermittent treatment method has been found to be superior in many parameters.

J Nutr. 2004 Feb;134(2):348-56.

Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelminthic treatment improves growth, appetite and anemia in Zanzibari preschool children.

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Iron deficiency and helminth infections are two common conditions of children in developing countries. The consequences of helminth infection in young children are not well described, and the efficacy of low dose iron supplementation is not well documented in malaria-endemic settings. A 12-mo randomized, placebo controlled, double-blind trial of 10 mg daily iron

and/or mebendazole (500 mg) every 3 mo was conducted in a community-based sample of 459 Zanzibari children age 6-71 mo with hemoglobin > 70 g/L at baseline. The trial was designed to examine treatment effects on growth, anemia and appetite in two age subgroups. **Iron did not affect growth retardation, hemoglobin concentration or mild or moderate anemia (hemoglobin < 110 g/L or < 90 g/L, respectively), but iron significantly improved serum ferritin and erythrocyte protoporphyrin. Mebendazole significantly reduced wasting malnutrition but only in children <30 mo old. The adjusted odds ratios (AORs) for mebendazole in this age group were 0.38 (95% CI: 0.16, 0.90) for weight-for-height less than -1 Z-score and 0.29 (0.09, 0.91) for small arm circumference. In children <24 mo old, mebendazole also reduced moderate anemia (AOR: 0.41, 0.18, 0.94). Both iron and mebendazole improved children's appetite, according to mothers' report. In this study, iron's effect on anemia was limited, likely constrained by infection, inflammation and perhaps other nutrient deficiencies. Mebendazole treatment caused unexpected and significant reductions in wasting malnutrition and anemia in very young children with light infections.** We hypothesize that incident helminth infections may stimulate inflammatory immune responses in young children, with deleterious effects on protein metabolism and erythropoiesis.

Zinc

Comment

The impact of zinc in the prevention and treatment of common diseases continues to be the subject of much discovery. Daily zinc given to low birth weight babies reduces diarrhoeal morbidity in the first year of life (see section on Low Birth Weight). Zinc supplementation results in substantial reductions in hospital mortality in children with protein-energy malnutrition. Further studies confirm that zinc decreases the duration and severity of diarrhoea and dehydration. Zinc sulphate injected into skin lesions has been shown to be effective in the treatment of cutaneous leishmaniasis in an RCT in adults (see section on Leishmaniasis). When zinc (20mg per day) was given to Bangladeshi children with acute respiratory infection there was a reduced risk of prolonged or severe pneumonia. One mechanism by which zinc might be effective in some infections is to increase the lymphocyte and immunoglobulin response to specific antigens, as shown in a study of children with Shigella.

J Trop Pediatr. 2003 Dec;49(6):353-60.

A randomized controlled study of the impact of dietary zinc supplementation in the management of children with protein-energy malnutrition in Lesotho. II: Special investigations.

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Protein-energy malnutrition (PEM) remains one of the common causes of morbidity and

mortality among children throughout the world. **The supplementation of 10 mg elemental zinc, as zinc sulphate, was evaluated in the management of PEM in a randomized, controlled, double-blind clinical trial in 300 children, aged 6-60 months (zinc, n = 150; control, n = 150) admitted to the Queen Elizabeth II Hospital, Maseru, Lesotho**. Supplementation and follow-up were done for 3 months post-discharge from the hospital. Both the supplemented and the control groups presented with biochemically determined zinc deficiency on presentation. **Despite supplementation the treated group only began to show evidence of biochemical increase in serum zinc at 60 days post-discharge from hospital.** This may represent the period of replacement of the total body zinc. **Zinc deficiency was more severe in those children in the control group that died after admission to hospital than those that survived, suggesting that low serum levels in children with PEM are associated with a poor prognosis.** Zinc did not emerge as a predicator of poor prognosis in the supplemented group as very few children died in this group. The supplemented group also made significant gains as far as albumin levels were concerned, which probably reflects rehabilitation of their malnutrition. The associated improvement in haematological parameters has not been described before and may be secondary to the decreased burden of disease in the supplemented group. These findings suggest that not only were significant benefits of zinc supplementation shown for morbidity in mortality of children in Lesotho with PEM, but these trends were also demonstrated on biochemical profiles.

J Trop Pediatr. 2003 Dec;49(6):340-52.

A randomized controlled study of the impact of dietary zinc supplementation in the management of children with protein-energy malnutrition in Lesotho. I: Mortality and morbidity.

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Protein-energy malnutrition (PEM) remains one of the common causes of morbidity and mortality among children throughout the world. The supplementation of 10 mg elemental zinc, as zinc sulphate, was evaluated in the management of PEM in a randomized, controlled double-blind clinical trial in 300 children, aged 6-60 months (zinc, n = 150; control, n = 150) admitted to the Queen Elizabeth II Hospital, Maseru, Lesotho. Supplementation and follow-up were done for 3 months post-discharge from the hospital. **Mortality during hospitalization was significantly lower in the zinc supplemented group (4.7 per cent), compared with 16.7 per cent in the control group.** The prevalence of morbidity was significantly higher in the control group at 1, 2, and 3 month's follow-up. **In the zinc supplemented group 58 per cent of the children were above the 80th percentile of expected weight-for-age 3 months after discharge, compared with 27.6 per cent in the control group**. Dietary zinc supplementation resulted in a significant reduction in diarrhoeal disease, respiratory morbidity, and episodes of clinical anaemia, skin infections, and fever as well as vomiting in children with PEM. These findings suggest that interventions to improve zinc intake in their management may be of benefit to Basotho children in Lesotho with PEM.

Int J Epidemiol. 2003 Dec;32(6):1098-102.

Effect of zinc supplementation on growth in West African children: a randomized double-blind placebo-controlled trial in rural Burkina Faso.

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OBJECTIVE: To analyse the effects of zinc supplementation on growth parameters in a representative sample of young children in rural Burkina Faso. Design Randomized, double-blind, placebo-controlled efficacy trial. Setting Eighteen villages in rural northwestern Burkina Faso. Subjects In all, **709 children aged 6-31 months were enrolled; 685 completed the trial. Intervention Supplementation with zinc (12.5 mg zinc sulphate) or placebo daily for 6 days a week for 6 months.** Outcomes Weight, length/height, mid-arm circumference, and serum zinc. RESULTS: In a representative subsample of study children, **72% were zinc-deficient at baseline. After supplementation, serum zinc increased in zinc-supplemented but not in control children of the subsample. No significant differences between groups were observed during follow-up regarding length/height, weight, mid-arm circumference, and z scores for height-for-age, weight-for-age, and weight-for-height.** CONCLUSIONS: We conclude that zinc supplementation does not have an effect of public health importance on growth in West African populations of young children with a high prevalence of malnutrition. Multinutrient interventions are likely to be more effective.

Am J Clin Nutr. 2004 Mar;79(3):457-65.

Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children.

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BACKGROUND: Zinc supplements reduce childhood morbidity in populations in whom zinc deficiency is common. In such populations, deficiencies in other micronutrients may also occur. OBJECTIVE: The objective was to determine whether the administration of other micronutrients with zinc modifies the effect of zinc supplementation on children's morbidity and physical growth. DESIGN: **Two hundred forty-six children aged 6-35 mo with persistent diarrhea were randomly assigned to 1 of 3 groups to receive a daily supplement of 10 mg Zn alone (Zn; n = 81), zinc plus vitamins and other minerals at 1-2 times recommended daily intakes (Zn+VM; n = 82), or placebo (n = 83) for approximately 6 mo after the diarrhea episode ended.** Morbidity information was collected on weekdays. Weight, length, and other anthropometric indicators were measured monthly, and plasma zinc and other indicators of micronutrient status were measured at baseline and 6 mo. RESULTS: Supplement

consumption was high (approximately 90%) in all groups, although slightly more vomiting was reported in the Zn+VM group (P < 0.0001, analysis of variance). The change in plasma zinc from baseline to 6 mo was greater in the 2 zinc groups (6.1, 27.3, and 16.2 micro g/dL in the placebo, Zn, and Zn+VM groups, respectively; P < 0.0001, analysis of variance). **The Zn group had fewer episodes of diarrhea, dysentery, and respiratory illness and a lower prevalence of fever and cough than did the Zn+VM group and a lower prevalence of cough than did the placebo group (P = 0.05). No significant effects of supplementation on growth were observed.** CONCLUSION: Morbidity was greater after supplementation with zinc plus multivitamins and minerals than it was after supplementation with zinc alone.

J Pediatr Gastroenterol Nutr. 2004 Jan;38(1):34-40.

Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial.

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OBJECTIVES: The authors evaluated the effect of zinc treatment as an adjunct to oral rehydration therapy on stool output and diarrheal duration in children with acute noncholera diarrhea with dehydration. METHODS: This double-blind, randomized, controlled trial was conducted at two urban hospitals in New Delhi. A total of 287 dehydrated male patients, ages 3 to 36 months, with diarrhea for <or= 72 hours were enrolled. They were assigned to zinc or placebo by a randomization scheme stratified by age (<or= or >12 months) and weight for height (65%-80% or >80% National Centre for Health Statistics median). **Participants in the zinc group received 15 mg (<or=12 months) or 30 mg (>12 months) elemental zinc daily in three divided doses for 14 days.** The main outcome measures were stool output and diarrheal duration. RESULTS: **Zinc treatment reduced total stool output (ratio of geometric means, 0.69; 95% confidence interval [CI]: 0.48, 0.99) and stool output per day of diarrhea (ratio of geometric means, 0.76; 95% CI: 0.59, 0.98). The risk of continued diarrhea was lower (relative hazards, 0.76; 95% CI: 0.59, 0.97) and the proportion of diarrheal episodes lasting >or= 5 days (odds ratio, 0.49; 95% CI: 0.25, 0.97) or >or= 7 days was less (odds ratio, 0.09; 95% CI: 0.01, 0.73) in the zinc group.** CONCLUSIONS: This study demonstrates a beneficial effect of zinc administered during acute diarrhea on stool output, diarrheal duration, and proportion of episodes lasting more than 7 days. The effects are large enough to merit routine use of zinc during acute diarrhea in developing countries.

Am J Clin Nutr. 2004 Mar;79(3):444-50.

Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis.

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BACKGROUND: Several studies showed benefits of long-term zinc supplementation on the incidence, severity, and duration of diarrhea and on the incidence of respiratory infections. Prolonged zinc supplementation also improves cell-mediated immunity in severely malnourished children. OBJECTIVE: We studied the effect of short-term zinc supplementation on intrinsic and specific immune and inflammatory responses in moderately malnourished children with acute shigellosis. DESIGN: A randomized, double-blind, placebo-controlled trial was conducted in **Shigella-infected children aged 12-59 mo. Elemental zinc (20 mg) and a multivitamin containing vitamins A and D, thiamine, riboflavin, nicotinamide, and calcium at twice the recommended dietary allowance were given daily for 2 wk to the zinc group (n = 28), whereas the multivitamin alone was given to the control group (n = 28).** Standard antibiotic therapy was given to all patients. RESULTS: Serum zinc concentrations increased in both groups during convalescence; however, zinc supplementation showed a significant effect. The lymphocyte proliferation response in the zinc group increased relative to that in the control group (P = 0.002), but no significant effects were seen on concentrations of cytokines (interleukin 2 and interferon gamma) released from mitogen-stimulated mononuclear cells or on concentrations of cytokines (interleukin 2, interferon gamma, and interleukin 1beta) in feces. Among the antigen [lipopolysaccharide and invasion plasmid-encoded antigen (Ipa)]-specific antibodies, plasma Ipa-specific immunoglobulin G responses at day 30 were significantly higher in the zinc group than in the control group. However, the 2 groups did not differ significantly in the other antigen-specific responses in plasma and stool. CONCLUSION: **A 14-d course of zinc supplementation during acute shigellosis increases the lymphocyte proliferation response and the Ipa-specific immunoglobulin G response.**

Lancet. 2004 May 22;363(9422):1683-8.

Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial.

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BACKGROUND: Pneumonia is a leading cause of morbidity and mortality in young children. Early reversal of severity signs--chest indrawing, hypoxia, and tachypnoea--improves outcome. We postulated that zinc, an acute phase reactant, would shorten duration of severe pneumonia and time in hospital. METHODS: In a double-blind placebo-controlled clinical trial in Matlab Hospital, Bangladesh, 270 children aged 2-23 months were randomised to receive elemental zinc (20 mg per day) or placebo, plus the hospital's standard antimicrobial management, until discharge. The outcomes were time to cessation of severe pneumonia (no chest indrawing, respiratory rate 50 per min or less, oxygen saturation at least 95% on room air) and discharge from hospital. Discharge was allowed when respiratory rate was 40 per minute or less for 24 consecutive hours while patients were maintained only on oral antibiotics. FINDINGS: **The group receiving zinc had reduced duration of severe pneumonia (relative hazard [RH]=0.70, 95% CI 0.51-0.98), including duration of chest indrawing (0.80, 0.61-1.05), respiratory rate more than 50 per min (0.74, 0.57-0.98), and hypoxia (0.79, 0.61-1.04), and**

overall hospital duration (0.75, 0.57-0.99). The mean reduction is equivalent to 1 hospital day for both severe pneumonia and time in hospital. All effects were greater when children with wheezing were omitted from the analysis. INTERPRETATION: Adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children, and could help reduce antimicrobial resistance by decreasing multiple antibiotic exposures, and lessen complications and deaths where second line drugs are unavailable.

Diarrhoea prevention

Comment

This year studies have proved that childhood diarrhoea can be prevented by encouraging household hand-washing with soap, use of low-cost water household filters, and by zinc supplementation for low birth weight babies (see section on Low Birth Weight).

JAMA. 2004 Jun 2;291(21):2547-54.

Effect of intensive handwashing promotion on childhood diarrhea in high-risk communities in Pakistan: a randomized controlled trial.

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CONTEXT: Washing hands with soap prevents diarrhea, but children at the highest risk of death from diarrhea are younger than 1 year, too young to wash their own hands. Previous studies lacked sufficient power to assess the impact of household handwashing on diarrhea in infants. OBJECTIVE: To evaluate the effect of promoting household handwashing with soap among children at the highest risk of death from diarrhea. DESIGN, SETTING, AND PARTICIPANTS: A cluster randomized controlled trial of 36 low-income neighborhoods in urban squatter settlements in Karachi, Pakistan. Field workers visited participating households at least weekly from April 15, 2002, to April 5, 2003. Eligible households located in the study area had at least 2 children younger than 15 years, at least 1 of whom was younger than 5 years. INTERVENTIONS: Weekly visits in 25 neighborhoods to promote handwashing with soap after defecation and before preparing food, eating, and feeding a child. Within intervention neighborhoods, 300 households (1523 children) received a regular supply of antibacterial soap and 300 households (1640 children) received plain soap. Eleven neighborhoods (306 households and 1528 children) comprised the control group. MAIN OUTCOME MEASURE: Incidence density of diarrhea among children, defined as the number of diarrheal episodes per 100 person-weeks of observation. RESULTS: **Children younger than 15 years living in households that received handwashing promotion and plain soap had a 53% lower incidence of diarrhea (95% confidence interval [CI], -65% to -41%) compared with children living in control neighborhoods.** Infants living in households that received handwashing promotion and plain soap had 39% fewer days with diarrhea (95% CI, -61% to -16%) vs infants living in control neighborhoods. Severely malnourished children (weight for age z score, <-3.0) younger than 5 years living in households that received

handwashing promotion and plain soap had 42% fewer days with diarrhea (95% CI, -69% to -16%) vs severely malnourished children in the control group. Similar reductions in diarrhea were observed among children living in households receiving antibacterial soap. CONCLUSION: In a setting in which diarrhea is a leading cause of child death, improvement in handwashing in the household reduced the incidence of diarrhea among children at high risk of death from diarrhea.

Am J Trop Med Hyg. 2004 Jun;70(6):651-7.

Reducing diarrhea through the use of household-based ceramic water filters: a randomized, controlled trial in rural Bolivia.

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Ceramic water filters have been identified as one of the most promising and accessible technologies for treating water at the household level. In a six-month trial, water filters were distributed randomly to half of the 50 participating households in a rural community in Bolivia; the remaining households continued to use customary water handling practices and served as controls. In four rounds of sampling following distribution of the filters, 100% of the 96 water samples from the filter households were free of thermotolerant coliforms compared with 15.5% of the control household samples. **Diarrheal disease risk for individuals in intervention households was 70% lower than for controls (95% confidence interval [CI] = 53-80%; P < 0.001). For children less than five years old, the reduction in risk was 83% (95% CI = 51-94%; P < 0.001).** These results show that affordable ceramic water filters enable low-income households to treat and maintain the microbiologic quality of their drinking water.

Cholera

Acta Paediatr. 2003 Jun;92(6):676-8.

Azithromycin in the treatment of cholera in children.

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AIM: To evaluate the efficacy of azithromycin in the treatment of cholera in children. METHODS: A double-blind, randomized, controlled clinical trial on 80 children with acute watery diarrhoea and moderate to severe dehydration compared the efficacy of azithromycin and erythromycin in treating cholera. Data were analysed for 56 patients who were stool culture positive for Vibrio cholerae. In conjunction with rehydration therapy, 29 patients

received azithromycin and 27 patients received erythromycin. Patients in the two treatment groups had comparable clinical and blood biochemical characteristics on admission. RESULTS: Patients who received azithromycin had significantly less stool output, shorter duration of diarrhoea and lower fluid intake compared with patients who received erythromycin. CONCLUSION: Azithromycin appears to be superior to erythromycin for treating cholera in children.

Nutrition

Comment

If school children are given a glass of milk each day they will have a lower risk of vitamin B12 deficiency, and greater height, weight and bone density. School milk programs should be encouraged. Some improvements to cognition may be achieved by supplementation with meat or high-energy containing foods, but the results are variable.

J Nutr. 2003 Nov;133(11 Suppl 2):3972S-3980S.

Kenyan school children have multiple micronutrient deficiencies, but increased plasma vitamin B-12 is the only detectable micronutrient response to meat or milk supplementation.

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Animal source foods (ASF) can provide micronutrients in greater amounts and more bioavailable forms compared to plant source foods, but their intake is low in many poor populations. However, the impact of ASF on micronutrient status of undernourished populations has not been assessed. **Supplemental meat (60-85 g/d), milk (200-250 mL/d) or energy (isocaloric with the meat and milk, 240-300 kcal/d) were randomly assigned to 555 undernourished school children aged 5-14 y in a rural malaria-endemic area of Kenya, at one school meal daily for one school year. Blood and stool samples were collected at baseline and after 1 y to assess stool parasites, malaria, hemoglobin, serum or plasma C-reactive protein, ferritin, iron, zinc, copper, vitamin B-12, folate and retinol, and erythrocyte riboflavin. At baseline, there was a high prevalence of micronutrient deficiencies (iron, zinc, vitamins A and B-12 and riboflavin), yet plasma ferritin was low in few children, and none had low serum copper. At the end of the year of supplementation, plasma vitamin B-12 concentrations were significantly increased in children fed the Meat or Milk meal; prevalence of severe plus moderate deficiency fell from 80.7% at baseline to 64.1% in the Meat group and from 71.6 to 45.1% in the Milk group, respectively.** No significant improvement was observed in the status of other micronutrients compared to the Energy and Control groups, although malaria and other infections may have obscured effects. **Supplementation with small amounts of meat or milk reduced the high prevalence of vitamin B-12 deficiency in these children.**

J Nutr. 2003 Nov;133(11 Suppl 2):3965S-3971S.

The impact of dietary intervention on the cognitive development of Kenyan school children.

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Previous observational studies in developing countries have suggested that diet quality, particularly increased animal source food (ASF) consumption, is positively associated with child cognitive development. This report presents findings from a study in rural Kenya, designed to test the impact of three different diets on the cognitive development of school children. Twelve schools with a total of 555 Standard 1 children (equivalent to U.S. Grade 1) were randomized to one of four feeding interventions: Meat, Milk, Energy or Control (no feeding). Feeding continued for seven school terms (21 mo), and cognitive tests were administered before the commencement of feeding and during every other term of feeding. Hierarchical linear random effects models and associated methods were used to examine the effects of treatment group on changes in cognitive performance over time. Analyses revealed that children receiving supplemental food with meat significantly outperformed all other children on the Raven's Progressive Matrices. Children supplemented with meat, and children supplemented with energy, outperformed children in the Control group on tests of arithmetic ability. There were no group differences on tests of verbal comprehension. **Results suggest that supplementation with animal source food has positive effects on Kenyan children's cognitive performance. However, these effects are not equivalent across all domains of cognitive functioning, nor did different forms of animal source foods produce the same beneficial effects.** Implications of these findings for supplementation programs in developing countries are discussed.

J Nutr. 2003 Nov;133(11 Suppl 2):3941S-3949S.

Animal source foods improve dietary quality, micronutrient status, growth and cognitive function in Kenyan school children: background, study design and baseline findings.

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A previous longitudinal three-country study in Egypt, Kenya and Mexico found significant positive associations between intake of animal source foods (ASF) and growth, cognitive development and physical activity. To test for a causal relationship, a controlled school feeding intervention study was designed to test the hypotheses that ASF would improve micronutrient status, growth and cognitive function in Kenyan primary school children. Twelve rural Kenyan schools with 554 children were randomized to four feeding interventions using a local vegetable stew as the vehicle. The groups were designated as Meat, Milk, Energy and Control, who received no feedings. Feeding was carried out on school days for seven terms during 21 mo. Preintervention baseline measures included nutritional status, home food intake, anthropometry, biochemical measures of micronutrient status, malaria, intestinal parasites, health status and cognitive and behavioral measures. The measurements of each child were repeated at intervals over 2 y. Baseline data revealed stunting and underweight in

approximately 30% of children and widespread inadequate intakes and/or biochemical evidence of micronutrient deficiencies, particularly of iron, zinc, vitamins A and B-12, riboflavin and calcium. Little or no ASF were eaten and fat intake was low. Malaria was present in 31% of children, and hookworm, amebiasis and giardia were widely prevalent. The outcomes measured were rates of change or increase during the intervention in cognitive function, growth, physical activity and behavior and micronutrient status. Hierarchical linear random effects modeling was used for analysis of outcomes.

Br J Nutr. 2004 Jul;92(1):159-68.

School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10-12 years in Beijing.

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A 2-year milk intervention trial was carried out with 757 girls, aged 10 years, from nine primary schools in Beijing (April 1999 - March 2001). Schools were randomised into three groups: group 1, 238 girls consumed a carton of 330 ml milk fortified with Ca on school days over the study period; group 2, 260 girls received the same quantity of milk additionally fortified with 5 or 8 microg cholecalciferol; group 3, 259 control girls. Anthropometric and bone mineralisation measurements, as well as dietary, health and physical-activity data, were collected at baseline and after 12 and 24 months of the trial. Over the 2-year period the consumption of this milk, with or without added cholecalciferol, led to significant increases in the changes in height (> or =0.6 %), sitting height (> or =0.8 %), body weight (> or 2.9 %), and (size-adjusted) total-body bone mineral content (> or =1.2 %) and bone mineral density (> or =3.2 %). Those subjects receiving additional cholecalciferol compared with those receiving the milk without added 25-hydoxycholecalciferol had significantly greater increases in the change in (size-adjusted) total-body bone mineral content (2.4 v. 1.2 %) and bone mineral density (5.5 v. 3.2 %). The milk fortified with cholecalciferol significantly improved vitamin D status at the end of the trial compared with the milk alone or control groups. It is concluded that an increase in milk consumption, e.g. by means of school milk programmes, would improve bone growth during adolescence, particularly when Ca intake and vitamin D status are low.

Neurocysticercosis

Epilepsia. 2003 Nov;44(11):1397-401.

Short course of prednisolone in Indian patients with solitary cysticercus granuloma and new-onset seizures.

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PURPOSE: To evaluate the role of a short course of oral corticosteroids in Indian patients with solitary cysticercus granuloma with seizures. METHODS: In this open-label, randomized, prospective follow-up study, 97 patients with new-onset seizures and a single enhancing computed tomography (CT)-detected lesion of cysticercosis were randomly divided in two groups to receive either antiepileptic monotherapy alone (n = 48) or antiepileptic monotherapy with prednisolone (n = 49). The patients in the latter group received prednisolone, 1 mg/kg/day for 10 days, followed by tapering over next 4 days. The patients were followed up for 6 months. Repeated CT scans were performed after 1 and 6 months. RESULTS: The majority of patients were young. Simple partial seizure, with or without secondary generalization, was the commonest seizure type encountered. Follow-up CT scans at 1 and 6 months demonstrated a significantly better response for prednisolone as far as complete resolution of CT lesion was concerned. Kaplan-Meier analysis suggested significantly less probability of seizure recurrence for prednisolone-treated patients. **At 6 months, Kaplan-Meier estimated risk of seizure after first seizure was 2% in prednisolone-treated patients in comparison to 13% for those who were not given prednisolone.** CONCLUSIONS: **Short-term prednisolone therapy helps in rapid resolution of solitary cysticercus granuloma in Indian patients with new-onset seizures.** Resolution of lesions is associated with improved seizure-related prognosis.

Low birth weight

Comment

How to improve the quality of survival becomes increasingly important as more low birth weight babies survive in developing countries. This year there are three RCTs addressing this: the impact of zinc on diarrhoea morbidity, and home visits to encourage maternal-infant interaction had a positive effect on cognition and behaviour. Zinc supplementation had no effect on cognition in LBW babies in India.

Pediatrics. 2003 Dec;112(6 Pt 1):1327-32.

Impact of zinc supplementation on diarrheal morbidity and growth pattern of low birth weight infants in kolkata, India: a randomized, double-blind, placebo-controlled, community-based study.

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OBJECTIVE: To assess the impact of zinc supplementation on diarrheal morbidity and growth pattern of low birth weight (LBW) infants. METHODOLOGY: In a randomized, double-blind, placebo-controlled, community-based study conducted in the Tiljala slum of eastern Kolkata, India, between 1999 and 2001, **a birth cohort of 100 LBW infants was randomly allocated into either an intervention group receiving 1 mL daily dose of 5 mg of elemental zinc as zinc sulfate in vitamin B complex-based syrup or a placebo group receiving an identical placebo of 1 mL of vitamin-based syrup from birth up to 1 completed year of age. Active weekly surveillance was conducted for detection of diarrhea.** Anthropometric measurements of each child were recorded once every month as close to the child's birth date as possible. Data were analyzed by using statistical software packages SPSSPC+ 4.0 (SPSS, Inc, Chicago, IL) and Epi Info 6.0 (Centers for Disease Control and Prevention, Atlanta, GA). RESULTS: **Among the zinc-supplemented group, diarrheal incidence of 1.36 episodes per child per year were observed, whereas it was 1.93 episodes per child per year among the placebo group, giving a relative risk of 1.4 (95% confidence interval: 1.02-2.00). Linear growth and weight for age showed significant differences between the supplemented and placebo groups only at the end of 1 year.** Interestingly, the impact of zinc supplementation was masked to a large extent by the protective action of breastfeeding. CONCLUSIONS: The study showed that zinc supplementation had a beneficial impact on the incidence of diarrhea and also weight gain among LBW infants.

Pediatrics. 2004 May;113(5):1297-305.

Cognitive and motor development among small-for-gestational-age infants: impact of zinc supplementation, birth weight, and caregiving practices.

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OBJECTIVE: Infants who are born small for gestational age (SGA) are at risk for developmental delays, which may be related to deficiencies in zinc, an essential trace metal, or to deficiencies in their ability to elicit caregiver responsiveness (functional isolation hypothesis). The objective of this study was to evaluate at 6 and 10 months of age the impact of a 9-month supplementation trial of 5 mg of zinc on the development and behavior of infants who were born SGA and to evaluate infants' ability to elicit responsive caregiver behavior. METHODS: **A randomized, controlled trial of zinc supplementation was conducted among 200 infants in a low-income, urban community in Delhi, India.** Infants were recruited when they were full term (>36 weeks) and SGA (birth weight <10th percentile weight-for-gestational age). Infants were randomized to receive daily supplements of a micronutrient mix (folate, iron, calcium, phosphorus, and riboflavin) with or without 5 mg of zinc sulfate. The supplement was administered by field workers daily from 30 days to 9 months of age. At 6 and 10 months, infant development and behavior were measured in a clinical setting using the Bayley Scales of Infant Development II. Caregiver responsiveness, observed on an Indian version of the Home Observation for Measurement of the Environment scale, was measured during a home visit at 10 months. During both the clinic and home visits, caregivers reported on their infant's temperament. RESULTS: There were no direct effects of zinc supplementation on the infants' development or behavior at either 6 or 10 months. In a subgroup analysis among the zinc-supplemented infants, lower birth weight infants were perceived to be more temperamentally difficult than higher weight infants; in the control group, birth weight was not associated with temperament. Heavier birth weight infants had better scores on all measures of development and behavior at 6 months and on changes in mental and motor development from 6 to 10 months, compared with lighter birth weight infants. Boys had better weight gain and higher scores on mental development and emotional regulation than girls. Infants who were from families of higher socioeconomic status (indexed by parental education, house size, and home ownership) had higher scores on mental development and orientation/engagement (exploratory behavior) than infants who were from families of lower socioeconomic status. In keeping with the functional isolation hypothesis, caregiver responsiveness was associated with infant irritability, controlling for socioeconomic status, gender, birth weight, and weight gain. Responsive mothers were more likely to perceive their infants to be temperamentally easy than less responsive mothers. CONCLUSION: Possible explanations for the lack of effects of zinc supplementation on infant development and behavior include 1) subtle effects of zinc supplementation that may not have been detected by the Bayley Scales, 2) interference with other nutritional deficiencies, or 3) no impact of zinc deficiency on infants' development and behavior. The link between birth weight and irritability among infants in the zinc supplementation group suggests that the response to zinc supplementation may differ by birth weight, with irritability occurring among the most vulnerable infants. Longer term follow-up studies among zinc-supplemented infants are needed to examine whether early supplementation leads to developmental or behavioral changes that have an impact on school-age performance. The relationship between infant irritability and low maternal responsiveness lends support to the functional isolation

hypothesis and the importance of asking caregivers about infant temperament.

J Pediatr. 2003 Nov;143(5):634-9.

A randomized controlled trial of a home-visiting intervention on cognition and behavior in term low birth weight infants.

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OBJECTIVES: To determine whether early psychosocial intervention with low birth weight term (LBW-T) infants improved cognition and behavior and to compare LBW-T with normal birth weight (NBW) infants. STUDY DESIGN: A randomized controlled trial was carried out in Kingston, Jamaica, with 140 LBW-T infants (weight<2500 g). The intervention comprised weekly home visits by paraprofessionals for the first 8 weeks of life aimed at improving maternal-child interaction. LBW-T and 94 matched NBW (weight 2500 to 4000 g) infants were recruited from the main maternity hospital. Main outcome measures were problem solving (2 means-end tests: cover and support) and 4 behavior ratings at 7 months. Analyses used were the t test for intervention effects and multiple regression to compare LBW and NBW infants. RESULTS: LBW-T intervened infants had higher scores than LBW-T control infants on the cover test (P<.05) and were more cooperative (P<.01) and happy (P<.05). LBW-T control infants had poorer scores on both the cover (P<.001) and support tests (P<.01), vocalized less (P<.02), and were less cooperative (P<.001), happy (P<.02), and active (P<.02) than NBW infants. LBW-T intervened infants had lower scores than NBW infants only on the support test (P<.05). CONCLUSIONS: Early low-cost intervention can improve cognition and behavior of LBW-T infants in developing countries.

Acute respiratory infection

Comment

The high proportion (23%) of children in this study with RSV bronchiolitis reduces the power to say that 3 days and 5 days are equivalent, especially as the definition of clinical failure included the development of chest in-drawing and tachypnoea beyond 3 days, both of which are very common in infants with bronchiolitis. The mortality was 0 in both groups. Note that RSV isolation was a significant risk factor for failure of treatment. What we need to know is the differences in outcome if the children with wheeze are excluded.

BMJ. 2004 Apr 3;328(7443):791. Epub 2004 Mar 16.

Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial.

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OBJECTIVE: To assess the efficacy of three days versus five days of treatment with oral amoxicillin for curing non-severe pneumonia in children. DESIGN: Randomised, double blind, placebo controlled multicentre trial. SETTING: Outpatient departments of seven referral hospitals in India. PARTICIPANTS: 2188 children aged 2-59 months, 1095 given three days of treatment and 1093 given five days. INTERVENTION: Oral amoxicillin 31-54 mg/kg/day in three divided doses. MAIN OUTCOME MEASURES: Treatment failure: defined as development of chest indrawing, convulsions, drowsiness, or inability to drink at any time; respiratory rate above age specific cut points on day 3 or later; or oxygen saturation by pulse oximetry < 90% on day 3. RESULTS: The clinical cure rates with three days and five days of treatment were 89.5% and 89.9%, respectively (absolute difference 0.4 (95% confidence interval--2.1 to 3.0)). Adherence to treatment regimen was 94% and 85% for three day and five day treatments, respectively. Loss to follow up was 5.4% by day 5. There were no deaths, 41 hospitalisations, and 36 minor adverse reactions. There were 225 (10.3%) clinical failures and 106 (5.3%) relapses, and rates were similar in both treatments. At enrollment, 513 (23.4%) children tested positive for respiratory syncytial virus, and Streptococcus pneumoniae and Haemophilus influenzae were isolated from the nasopharynx in 878 (40.4%) and 496 (22.8%) children, respectively. Clinical failure was associated with isolation of respiratory syncytial virus (adjusted odds ratio 1.95 (95% confidence interval 1.0 to 3.8)), excess respiratory rate of > 10 breaths/minute (2.89 (1.83 to 4.55)), and non-adherence with treatment at day 5 (11.57 (7.4 to 18.0)). CONCLUSIONS: Treatment with oral amoxicillin for three days was as effective as for five days in children with non-severe pneumonia.

Cochrane Database Syst Rev. 2003;(4):CD003257.

Symptomatic treatment of the cough in whooping cough.

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BACKGROUND: Whooping cough is an important cause of childhood morbidity and mortality. There are 20 to 40 million cases of whooping cough annually world-wide, 90% of which occur in developing countries, resulting in an estimated 200 to 300 000 fatalities each year. Much of the morbidity is due to the effects of the paroxysmal cough. Corticosteroids, salbutamol (beta 2 - adrenergic stimulant), and pertussis-specific immunoglobulin have been proposed as standard treatment for the cough. Antihistamines have also been administered. No systematic review of the effectiveness of any of these interventions or others has been performed. OBJECTIVES: To assess the effectiveness and safety of interventions used to reduce the severity of the coughing paroxysms in whooping cough in children and adults. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 2, 2003); MEDLINE (January 1966 to June 2003); EMBASE (1990 to June 2003) and LILACS (1982 to November 2001). We also scanned reference lists of identified trials and contacted authors of identified trials and relevant pharmaceutical companies. SELECTION CRITERIA: Randomised and quasi-randomised controlled trials of any intervention aimed at suppressing the cough in whooping cough; excluding antibiotics and vaccines. DATA COLLECTION AND ANALYSIS: Two reviewers independently selected studies and extracted data. Our primary outcome was frequency of paroxysms of coughing. Secondary outcomes were frequency of vomiting, frequency of whoop, frequency of cyanosis, development of serious complications, mortality from any cause, side effects due to medication, admission to hospital and duration of hospital stay. Disagreements were resolved by discussion. MAIN RESULTS: Nine studies satisfied the inclusion criteria but four had insufficient data for meta - analysis of pre-specified outcomes. Studies were small and poorly reported. The largest study had a sample size of 49 and the smallest study 18. All studies were performed in industrialised settings.Eligible studies assessed diphenhyramine, pertussis immunoglobulin, dexamethasone and salbutamol. No statistically significant benefit was found for any of the interventions. **Diphenhydramine did not change coughing spells (mean increase of coughing spells per 24 hours 1.9 with 95%CI - 4.7 to 8.5) and pertussis immunoglobulin no change in hospital stay (0.7 days 95% CI -3.8 to 2.4), and a mean reduction of 3.1 whoops per 24 hours [95% CI -6.2; 0.02]. Dexamethasone did not show a clear decrease in hospital stay (-3.5 days 95% CI - 15.3 to 8.4) and salbutamol showed no change in coughing paroxysms per 24 hours [-0.22 95% CI - 4.13 to 3.69].** REVIEWER'S CONCLUSIONS: Insufficient evidence exists to draw conclusions about the effects of any intervention for the cough in whooping cough.

Malaria prevention

Comment

A meta-analysis has confirmed that insecticide impregnated bed nets are highly effective in reducing the incidence of severe malaria and mortality, and a 6-year follow-up of an RCT has shown that the effect on mortality (a 22% reduction in all-cause mortality in the first few years) is sustained after up to 6 years of bed-net use by communities. Mass antimalarial drug administration in Gambia had no effect on subsequent malaria incidence, but in a refugee camp in Afghanistan use of DEET impregnated soap reduced the number of presentations with falciparum malaria. This is the second RCT this year showing that soap has public health benefit (see section on Diarrhoea prevention).

Vaccine. 2003 Dec 8;22(1):30-41.

Safety and immunogenicity of a three-component blood-stage malaria vaccine (MSP1, MSP2, RESA) against Plasmodium falciparum in Papua New Guinean children.

Genton B, Al-Yaman F, Betuela I, Anders RF, Saul A, Baea K, Mellombo M, Taraika J, Brown GV, Pye D, Irving DO, Felger I, Beck HP, Smith TA, Alpers MP.

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Combination B is a malaria vaccine that comprises recombinant Plasmodium falciparum (P. falciparum) blood-stage proteins MSP1, MSP2 and RESA, formulated with the adjuvant Montanide ISA 720. A phase I-IIb double-blind randomised placebo-controlled trial was undertaken in 120 children aged 5-9 years. Subjects were randomised in four groups: (i) No sulphadoxine-pyrimethamine (SP)+vaccine, (ii) No SP+placebo, (iii) SP+vaccine, (iv) SP+placebo. 15 microg of each protein were given in the thigh, at both first and second injection (4 weeks apart). The placebo was adjuvant emulsified with saline. No serious or severe AEs occurred. Moderate AEs were seen in 3% of the vaccine and 3% of the placebo recipients after first injection and in 12 and 10% after second injection. The vaccine induced significant antibody responses to all three antigens but triggered an IFN-gamma response to MSP1 only. At Week 12, the IFN-gamma response to MSP1 was substantially higher in the vaccine group where No SP had been given. Combination B proved to be safe and immunogenic in children aged 5-9 years. **Vaccine immunogenicity was neither impaired by circulating parasites nor increased after pre-treatment with SP and pre-treatment is not advisable in future trials of malaria vaccines, at least for those including blood-stage antigens.**

JAMA. 2004 Jun 2;291(21):2571-80.

Sustainability of reductions in malaria transmission and infant mortality in western Kenya with use of insecticide-treated bednets: 4 to 6 years of follow-up.

Lindblade KA, Eisele TP, Gimnig JE, Alaii JA, Odhiambo F, ter Kuile FO, Hawley WA, Wannemuehler KA, Phillips-Howard PA, Rosen DH, Nahlen BL, Terlouw DJ, Adazu K, Vulule JM, Slutsker L.

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CONTEXT: Insecticide-treated bednets reduce malaria transmission and child morbidity and mortality in short-term trials, but this impact may not be sustainable. **Previous investigators have suggested that bednet use might paradoxically increase mortality in older children through delayed acquisition of immunity to malaria.** OBJECTIVES: To determine whether adherence to and public health benefits of insecticide-treated bednets can be sustained over time and whether bednet use during infancy increases all-cause mortality rates in older children in an area of intense perennial malaria transmission. DESIGN AND SETTING: A community randomized controlled trial in western Kenya (phase 1: January 1997 to February 2000) followed by continued surveillance of adherence, entomologic parameters, morbidity indicators, and all-cause mortality (phase 2: April 1999 to February 2002), and extended demographic monitoring (January to December 2002). PARTICIPANTS: A total of 130,000 residents of 221 villages in Asembo and Gem were randomized to receive insecticide-treated bednets at the start of phase 1 (111 villages) or phase 2 (110 villages). MAIN OUTCOME MEASURES: Proportion of children younger than 5 years using insecticide-treated bednets, mean number of Anopheles mosquitoes per house, and all-cause mortality rates. RESULTS: Adherence to bednet use in children younger than 5 years increased from 65.9% in phase 1 to 82.5% in phase 2 (P<.001). After 3 to 4 years of bednet use, the mean number of Anopheles mosquitoes per house in the study area was 77% lower than in a neighboring area without bednets (risk ratio, 0.23; 95% confidence interval [CI], 0.15-0.35). All-cause mortality rates in infants aged 1 to 11 months were significantly reduced in intervention villages during phase 1 (hazard ratio [HR], 0.78; 95% CI, 0.67-0.90); low rates were maintained during phase 2. Mortality rates did not differ during 2002 (after up to 6 years of bednet use) between children from former intervention and former control households born during phase 1 (HR, 1.01; 95% CI, 0.86-1.19). CONCLUSIONS: **The public health benefits of insecticide-treated bednets were sustained for up to 6 years. There is no evidence that bednet use from birth increases all-cause mortality in older children in an area of intense perennial transmission of malaria.**

Cochrane Database Syst Rev. 2004;(2):CD000363.

Insecticide-treated bed nets and curtains for preventing malaria.

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BACKGROUND: Malaria is an important cause of illness and death in many parts of the world, especially in sub-Saharan Africa. There has been a renewed emphasis on preventive measures at community and individual levels. Insecticide-treated nets (ITNs) are the most prominent malaria preventive measure for large-scale deployment in highly endemic areas.

OBJECTIVES: To assess the impact of insecticide-treated bed nets or curtains on mortality, malarial illness (life-threatening and mild), malaria parasitaemia, anaemia, and spleen rates. SEARCH STRATEGY: I searched the Cochrane Infectious Diseases Group trials register (January 2003), CENTRAL (The Cochrane Library, Issue 1, 2003), MEDLINE (1966 to October 2003), EMBASE (1974 to November 2002), LILACS (1982 to January 2003), and reference lists of reviews, books, and trials. I handsearched journals, contacted researchers, funding agencies, and net and insecticide manufacturers. SELECTION CRITERIA: Individual and cluster randomized controlled trials of insecticide-treated bed nets or curtains compared to nets without insecticide or no nets. Trials including only pregnant women were excluded. DATA COLLECTION AND ANALYSIS: The reviewer and two independent assessors reviewed trials for inclusion. The reviewer assessed trial methodological quality and extracted and analysed data. MAIN RESULTS: Fourteen cluster randomized and eight individually randomized controlled trials met the inclusion criteria. Five trials measured child mortality: ITNs provided 17% protective efficacy (PE) compared to no nets (relative rate 0.83, 95% confidence interval (CI) 0.76 to 0.90), and 23% PE compared to untreated nets (relative rate 0.77, 95% CI 0.63 to 0.95). **About 5.5 lives (95% CI 3.39 to 7.67) can be saved each year for every 1000 children protected with ITNs. In areas with stable malaria, ITNs reduced the incidence of uncomplicated malarial episodes in areas of stable malaria by 50% compared to no nets, and 39% compared to untreated nets; and in areas of unstable malaria: by 62% for compared to no nets and 43% compared to untreated nets for Plasmodium falciparum episodes, and by 52% compared to no nets and 11% compared to untreated nets for P. vivax episodes. When compared to no nets and in areas of stable malaria, ITNs also had an impact on severe malaria (45% PE, 95% CI 20 to 63), parasite prevalence (13% PE), high parasitaemia (29% PE), splenomegaly (30% PE), and their use improved the average haemoglobin level in children by 1.7% packed cell volume.** REVIEWERS' CONCLUSIONS: ITNs are highly effective in reducing childhood mortality and morbidity from malaria. Widespread access to ITNs is currently being advocated by Roll Back Malaria, but universal deployment will require major financial, technical, and operational inputs

Trans R Soc Trop Med Hyg. 2003 Mar-Apr;97(2):217-25.

The effect of mass administration of sulfadoxine-pyrimethamine combined with artesunate on malaria incidence: a double-blind, community-randomized, placebo-controlled trial in The Gambia.

von Seidlein L, Walraven G, Milligan PJ, Alexander N, Manneh F, Deen JL, Coleman R, Jawara M, Lindsay SW, Drakeley C, De Martin S, Olliaro P, Bennett S, Schim van der Loeff M, Okunoye K, Targett GA, McAdam KP, Doherty JF, Greenwood BM, Pinder M.

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A double-blind, community-randomized, placebo-controlled trial was conducted in a rural area of The Gambia between June and December 1999 to test whether a reduction in the infectious reservoir can reduce malaria transmission. Overall 14,017 (85%) individuals living in the study area were treated with either placebo or sulfadoxine-pyrimethamine (SP) combined with a single dose of artesunate (AS). Following the mass drug administration (MDA) 1375 children aged 6 months to 10 years were kept under surveillance for clinical malaria in 18 villages

throughout the 1999 malaria transmission season. During a 20-week surveillance period 637 episodes of malaria were detected. **The mean incidence rate was 2.5/100 child-weeks in the placebo villages, and 2.3/100 child-weeks in villages that received SP + AS. The mean rate ratio, adjusted for individual and village-level covariates, was 0.91 (95% CI 0.68-1.22, P = 0.49).** During the first 2 months of surveillance, the malaria incidence was lower in treated villages. After 2 months the incidence was slightly higher in the MDA group but this was not statistically significant. Overall, no benefit of the MDA could be detected. The reason for the absence of an impact on malaria transmission is probably the very high basic reproductive number of malaria, and the persistence of mature gametocytes, which are not affected by AS treatment.

Trop Med Int Health. 2004 Mar;9(3):335-42

DEET mosquito repellent provides personal protection against malaria: a household randomized trial in an Afghan refugee camp in Pakistan.

Rowland M, Downey G, Rab A, Freeman T, Mohammad N, Rehman H, Durrani N, Reyburn H, Curtis C, Lines J, Fayaz M.

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Synthetic repellents based on di-ethyl 3-methyl benzamide (DEET) are a popular method of obtaining protection from mosquitoes and yet clear evidence for a protective effect against malaria has hitherto never been convincingly demonstrated. A household randomized trial was undertaken among a study population of 127 families (25%) in an Afghan refugee village in Pakistan to compare the efficacy of repellent soap (Mosbar containing 20% DEET and 0.5% permethrin) vs. a placebo lotion. Cases of falciparum and vivax malaria were detected by passive case detection at the camp's clinic. At the end of the 6 month trial 3.7% (23 of 618) of individuals in the Mosbar group had presented with one or more episodes of falciparum malaria compared with 8.9% (47 of 530) of the placebo group (odds ratio 0.44, 95% CI 0.25-0.76). 16.7% of the Mosbar group (103 of 618) presented with vivax malaria compared with 11.7% (62 of 530) of the placebo group, and thus no effect was shown against vivax malaria (odds ratio 1.29, 95% CI 0.86-1.94). A considerable proportion of individuals (22%) had presented with vivax malaria during the 7 months leading up to the trial and thus any intervention effect would be partially masked by relapsed infections. The distribution of mosquitoes among households was broadly similar between Mosbar and placebo groups. The repellent was popularly received and very few side-effects were reported. There is a case for giving repellents more prominence in public health as a preventive measure in regions where vectors bite in the early evening or in emergency situations such as epidemics or newly established refugee camps.

Malaria: treatment of uncomplicated *P. falciparum* disease

Comment

Almost all regions of the world are facing the problem of chloroquine-resistant malaria, and some parts of Africa are facing sulfadoxine/pyrimethamine-resistance. This year 10 RCTs of various antimalarials and combinations have been published from Mozambique, Congo, Gabon, Gambia, Sudan, Uganda, Bolivia, Ecuador and Vietnam. Combination therapies are more effective than single agents, but the beneficial effects of drug combinations that include chloroquine may be transient in areas in areas of high transmission. Agents that have been effectively used in combination include artesunate, SP, fosmidomycin and clindamycin, mefloquine, chlorproguanil and dapsone, and other artemisinin derivatives. A meta-analysis of 16 trials using addition of 3 days of artesunate to existing first-line drug regimens showed an 80% reduction in the incidence of parasitological failure at 14 days. All artesunate-combination trials showed a benefit.

Trop Med Int Health. 2004 Feb;9(2):200-8.

Efficacy of chloroquine, amodiaquine, sulphadoxine-pyrimethamine and combination therapy with artesunate in Mozambican children with non-complicated malaria.

Abacassamo F, Enosse S, Aponte JJ, Gomez-Olive FX, Quinto L, Mabunda S, Barreto A, Magnussen P, Ronn AM, Thompson R, Alonso PL.

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This paper reports a two-phase study in Manhica district, Mozambique: first we assessed the clinical efficacy and parasitological response of Plasmodium falciparum to chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ), then we tested the safety and efficacy in the treatment of uncomplicated malaria, of three combinations: AQ + SP, artesunate (AR) + SP and AQ + AR. Based on the WHO (1996, WHO/MAL/96.1077) in vivo protocol, we conducted two open, randomized, clinical trials. Children aged 6-59 months with axillary body temperature > or = 37.5 degrees C and non-complicated malaria were randomly allocated to treatment groups and followed up for 21 days (first and second trial) and 28 days (first trial). The therapeutic efficacy of AQ (91.6%) was better than that of SP (82.7%) and CQ (47.1%). After 14 days, 69% of the strains were parasitologically resistant to CQ, 21.4% to SP and 26% to AQ. Co-administration of AQ + SP, AR + SP and AQ + AR was safe and had 100% clinical efficacy at 14-day follow-up. The combination therapies affected rapid fever clearance time and reduced the incidence of gametocytaemia during follow-up.

Am J Trop Med Hyg. 2004 Feb;70(2):133-8.

Efficacy of sulfadoxine/pyrimethamine in the treatment of uncomplicated Plasmodium falciparum malaria in Republic of Congo.

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Congo is facing frequent failures of treatment of Plasmodium falciparum malaria with chloroquine (CQ), which is still recommended and used as a first-line drug. In Pointe-Noire and Brazzaville, the two largest cities that contain approximately 60% of the population of Congo, we compared the efficacy of CQ versus sulfadoxine/pyrimethamine (SP) for treatment of uncomplicated malaria in children 6-59 months old (mean = 33 months) using the standard World Health Organization (WHO) 14-day in vivo test in two phases between 1999 and 2002. Patients enrolled were randomly assigned to receive SP (25 mg/kg of sulfadoxine and 1.25 mg/kg of pyrimethamine) or CQ (25 mg/kg). In the first phase of the study, 46 patients were assigned to the CQ (n = 23) or SP (n = 23) groups in Pointe-Noire and 52 children were assigned to the CQ (n = 26) or to SP (n = 26) groups in Brazzaville. Results were interpreted according to the WHO lot quality assurance sampling method, and treatment failure rates for SP versus CQ were < 25% versus > 25% in both cities. In the second phase of the study, we accurately determined the actual proportion of treatment failures for SP in Brazzaville. Thus, in 75 of the 80 children enrolled and followed-up until day 14, no clinical or parasitologic failure was recorded and no serious adverse reaction was observed. Since the CQ treatment failure rate exceeds the unacceptable upper limit, SP seems well to be an appropriate alternative for the first-line treatment of uncomplicated P. falciparum malaria, at least in the settings of the present study.

J Infect Dis. 2004 Mar 1;189(5):901-8. Epub 2004 Feb 16

Fosmidomycin-clindamycin for Plasmodium falciparum Infections in African children.

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BACKGROUND: Fosmidomycin is a new antimalarial drug with a novel mechanism of action. Studies in Africa that have evaluated fosmidomycin as monotherapeutic agent demonstrated its excellent tolerance, but 3-times-daily treatment regimens of >or=4 days were required to achieve radical cure, prompting further research to identify and validate a suitable combination partner to enhance its efficacy. METHODS: We conducted a randomized, controlled, open-label study to evaluate the efficacy and safety of fosmidomycin combined with clindamycin (n=12; 30 and 5 mg/kg body weight every 12 h for 5 days, respectively), compared with fosmidomycin alone (n=12; 30 mg/kg body weight every 12 h for 5 days) and clindamycin alone (n=12; 5 mg/kg body weight every 12 h for 5 days) for the clearance of asymptomatic Plasmodium falciparum infections in schoolchildren in Gabon aged 7-14 years. RESULTS: Asexual parasites were rapidly cleared in children treated with fosmidomycin-clindamycin (median time, 18 h) and fosmidomycin alone (25 h) but slowly in children treated with clindamycin alone (71 h; P=.004). However, only treatment with fosmidomycin-clindamycin

or clindamycin alone led to the radical elimination of asexual parasites as measured by day 14 and 28 cure rates of 100%. Asexual parasites reappeared by day 28 in 7 children who received fosmidomycin (day 14 cure rate, 92% [11/12; day 28 cure rate, 42% [5/12]). All regimens were well tolerated, and no serious adverse events occurred. CONCLUSION: The combination of fosmidomycin and clindamycin is well tolerated and superior to either agent on its own with respect to the rapid and radical clearance of P. falciparum infections in African children.

Trop Med Int Health. 2004 Jan;9(1):53-61.

Addition of artesunate to chloroquine for treatment of Plasmodium falciparum malaria in Gambian children causes a significant but short-lived reduction in infectiousness for mosquitoes.

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OBJECTIVES: Combination therapy using existing anti-malarials together with artesunate (AS) has been advocated as a method to slow the spread of drug resistance. We assessed the effect on Plasmodium falciparum transmissibility of the addition of AS to chloroquine (CQ) in an area of The Gambia where resistance to CQ is increasing. METHODS: Gambian children with acute uncomplicated P. falciparum malaria were treated with either CQ monotherapy (n=120) or the combination of CQ plus three doses of AS (CQ/AS; n=352). Post-treatment sexual-stage parasitaemia was assessed during a 4-week follow-up period. Experimental infections of Anopheles gambiae s.s. mosquitoes were performed with blood from patients who were carrying gametocytes 7 days after starting treatment (n=69). RESULTS: The addition of AS significantly reduced post-treatment prevalence and mean density of gametocytes in the first 14 days (day 7: 43.7% vs. 12.4%, 62.4/microl vs. 6.2/microl; day 14: 32.9% vs. 3.7%; 21.9/microl vs. 5.2/microl; CQ vs. CQ/AS), although by day 28 the benefits of the combination were substantially less marked (40.5% vs. 21.8%; 23.0/microl vs. 63.1/microl; CQ vs. CQ/AS). The duration of gametocyte carriage over the study period was significantly lower in the CQ/AS group (5.2 days vs. 1.5 days; CQ vs. CQ/AS). The estimated infectious proportion of children at day 7 was also lower in the combination group (19.2% vs. 3.4%; CQ vs. CQ/AS), as were the proportion of mosquitoes infected and mean oocyst density (11.5% vs. 0.9%; 0.3 vs. 0.01; CQ vs. CQ/AS). Treatment failure was associated with threefold and twofold higher gametocyte carriage rates during follow-up in CQ and CQ/AS groups, respectively ($P<0.001$ in both cases), and 26-fold and 2.3-fold higher intensity of infection at day 7 among CQ- and CQ/AS-treated children, respectively ($P=0.002$ and 0.30, respectively). CONCLUSION: The benefits of adding AS to CQ monotherapy in lowering gametocyte prevalence and density were transient, suggesting that the addition of AS delayed, but did not prevent, the emergence of gametocytes. This is consistent with our finding that treatment failure, and thus the presence of CQ-resistant parasites, was significantly associated with a higher gametocyte carriage rate in both treatment groups. At day 7, CQ monotherapy significantly favoured transmission of resistant infections, which showed an 11-fold greater intensity of transmission compared with infections that were successfully treated. In contrast, the combination of CQ/AS did not significantly favour resistant infections at day 7. We conclude that significant transmission-

reduction is achieved by the combination but is not maintained because of the recrudescence of CQ-resistant parasites.

Trans R Soc Trop Med Hyg. 2003 Mar-Apr;97(2):229-35.

Chloroquine, sulfadoxine-pyrimethamine and amodiaquine efficacy for the treatment of uncomplicated Plasmodium falciparum malaria in Upper Nile, south Sudan.

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The current first-line and second-line drugs for Plasmodium falciparum malaria in South Sudan, chloroquine and sulfadoxine-pyrimethamine (SP), were evaluated and compared with amodiaquine, in an MSF-Holland-run clinic in eastern Upper Nile, South Sudan from June to December 2001. Patients with uncomplicated malaria and fever were stratified by age group and randomly allocated to one of 3 treatment regimes. A total of 342 patients was admitted and followed for 14 d after treatment. The dropout rate was 10.2%. Of those who completed the study, 104 were treated with chloroquine (25 mg/kg, 3 d), 102 with SP (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine, single dose) and 101 with amodiaquine (25 mg/kg, 3 d). Adequate clinical response was observed in 88.5% of patients treated with chloroquine, 100% of patients treated with SP and 94.1% of patients treated with amodiaquine. In children aged < 5 years, the success rate was lower: 83.3% for chloroquine and 93.0% for amodiaquine. In adults no treatment failures were found, but children aged 5-15 years showed intermediate levels. In addition, we determined the initial genotypes of dhfr and dhps of 44 isolates from the SP-treated group and > 80% were found to be wild type for dhfr and 100% for dhps. Two percent of isolates had a single mutation and 16% had double mutations of dhfr. These data are in full agreement with the clinical effectiveness of SP. A change in malaria treatment protocols for South Sudan is recommended.

Trop Med Int Health. 2004 Jan;9(1):47-52.

The efficacy of chloroquine, sulfadoxine-pyrimethamine and a combination of both for the treatment of uncomplicated Plasmodium falciparum malaria in an area of low transmission in western Uganda.

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We conducted an efficacy study of chloroquine (CQ), sulfadoxine-pyrimethamine (SP) and a combination of both (SP+CQ) for the treatment of uncomplicated malaria in an area of low transmission with low drug pressure. On day 3, fever clearance was 97.4% (95% CI, 86.8-99.9), 100% (95% CI, 87.2-100) and 96.6% (95% CI, 82.2-99.9) in the CQ, SP and SP+CQ

groups, respectively, (P=0.65). On day 14, clinical success was 92.5% (95% CI, 79.6-98.4), 100% (95% CI, 87.2-100) and 100% (95% CI, 88.1-100) in the CQ, SP and CQ+SP groups, respectively. Clinical failure was seen in 7.5% with 5% (95% CI, 0.61-16.9) early treatment failure and 2.5% (95% CI, 0.06-13.2) late treatment failure of cases in the CQ group and 0% in the SP and SP+CQ groups. Parasitological resistance was observed at RI level in 10% (95% CI, 2.8-23.7), 18.5% (95% CI, 6.3-38.1) and 6.9% (95% CI, 0.85-22.8) for the CQ, SP and SP+CQ, respectively (P=0.37). There was no age-dependent difference in clinical failure or parasitological resistance in any of the treatment groups and prior CQ use within the last 2 weeks did not affect CQ treatment outcome. The findings of this study suggest that CQ is still effective for the treatment of uncomplicated malaria in this area of low transmission and SP. However, combination therapy of SP+CQ is recommended to delay the development SP resistance, and regular surveillance for emerging CQ and SP resistance is needed to plan for alternative antimalarial drug regimens.

Trop Med Int Health. 2004 Feb;9(2):217-21.

Efficacy of mefloquine and mefloquine-artesunate for the treatment of uncomplicated Plasmodium falciparum malaria in the Amazon region of Bolivia.

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We assessed the efficacy of mefloquine monotherapy and mefloquine-artesunate (MQ-AS) combination therapy for the treatment of Plasmodium falciparum malaria at four sites in the Bolivian Amazon region. Patients with uncomplicated P. falciparum infections between 5 and 60 years of age were randomly assigned to be treated with either MQ (15 mg/kg in a single oral dose) or MQ (15 mg/kg) plus AS (4 mg/kg daily for 3 days). A total of 143 patients were enrolled and followed for 28 days. None of the 73 patients who received MQ alone or the 70 patients who received MQ-AS combination therapy had recurrences of parasitaemia during the 28-day follow-up period. Asexual parasite densities fell significantly more rapidly and the proportion of patients with gametocytes was significantly lower on days 7-28 in patients treated with MQ-AS than in those treated with MQ alone. All patients tolerated the medications well. After this study, the Bolivian Ministry of Public Health changed its treatment policy for uncomplicated P. falciparum malaria in the Amazon region to combination therapy with MQ-AS to slow or prevent the development of resistance.

Lancet. 2004 Jan 3;363(9402):9-17.

Artesunate combinations for treatment of malaria: meta-analysis.

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BACKGROUND: Addition of artemisinin derivatives to existing drug regimens for malaria could reduce treatment failure and transmission potential. We assessed the evidence for this hypothesis from randomised controlled trials. METHODS: We undertook a meta-analysis of individual patients' data from 16 randomised trials (n=5948) that studied the effects of the addition of artesunate to standard treatment of Plasmodium falciparum malaria. We estimated odds ratios (OR) of parasitological failure at days 14 and 28 (artesunate combination compared with standard treatment) and calculated combined summary ORs across trials using standard methods. FINDINGS: For all trials combined, parasitological failure was lower with 3 days of artesunate at day 14 (OR 0.20, 95% CI 0.17-0.25, n=4504) and at day 28 (excluding new infections, 0.23, 0.19-0.28, n=2908; including re-infections, 0.30, 0.26-0.35, n=4332). Parasite clearance was significantly faster (rate ratio 1.98, 95% CI 1.85-2.12, n=3517) with artesunate. In participants with no gametocytes at baseline, artesunate reduced gametocyte count on day 7 (OR 0.11, 95% CI 0.09-0.15, n=2734), with larger effects at days 14 and 28. Adding artesunate for 1 day (six trials) was associated with fewer failures by day 14 (0.61, 0.48-0.77, n=1980) and day 28 (adjusted to exclude new infections 0.68, 0.53-0.89, n=1205; unadjusted including reinfections 0.77, 0.63-0.95, n=1958). In these trials, gametocytes were reduced by day 7 (in participants with no gametocytes at baseline 0.11, 0.09-0.15, n=2734). The occurrence of serious adverse events did not differ significantly between artesunate and placebo. INTERPRETATION: The addition of 3 days of artesunate to standard antimalarial treatments substantially reduce treatment failure, recrudescence, and gametocyte carriage.

Acta Trop. 2003 Dec;89(1):47-53.

Randomised efficacy and safety study of two 3-day artesunate rectal capsule/mefloquine regimens versus artesunate alone for uncomplicated malaria in Ecuadorian children.

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The combination of artesunate and mefloquine is one of the most effective treatments against multidrug-resistant falciparum malaria. Experience in children is however limited. The objective of this study was to compare the efficacy and safety of two artesunate/mefloquine combinations with artesunate monotherapy in Ecuadorian children. A total of 150 children with an age between 2 and 12 years, confirmed to have uncomplicated falciparum malaria, were randomly selected and divided in three treatment groups of 50 patients each. Group 1 received 50 mg rectal capsules alone (40 mg/kg total dose) administered over 6 days. Group 2 received 50 mg rectal capsules (30 mg/kg total dose) for 3 days combined with mefloquine (20 mg/kg total dose) on day 1. Group 3 was treated with 50 mg rectal capsules (30 mg/kg total dose) for 3 days, combined with mefloquine on days 1 and 3 (15-17 mg/kg total dose). Patients were continuously followed up and controlled by clinical and laboratory examinations for 7 days as well as on days 14, 21 and 28. An additional parasite examination was performed at 2 months following therapy. Clearance of parasitaemia was comparable between treatment groups. These were 9.2, 9.2 and 8.3 h for Groups 1, 2 and 3, respectively. Cure rates at day 28 were 76, 96 and 94% and after 2 months 60, 88 and 80%, respectively. There were no adverse events (AEs) reported during the study. Vital signs and laboratory examinations revealed no changes of

clinical relevance. It can be concluded that the combination of artesunate rectal capsules with mefloquine is effective and safe. Starting concomitant administration already on day 1 is well tolerated. This combination significantly reduces the incidence of recrudescence compared to artesunate monotherapy. Comparing the two tested artesunate/mefloquine regimens, a total mefloquine dose of 20 mg/kg seems to be more effective compared to a total dose of 15-17 mg/kg. Further studies seem to be warranted.

Lancet. 2004 Jun 5;363(9424):1843-8.

Comparison of chlorproguanil-dapsone with sulfadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria in young African children: double-blind randomised controlled trial.

Alloueche A, Bailey W, Barton S, Bwika J, Chimpeni P, Falade CO, Fehintola FA, Horton J, Jaffar S, Kanyok T, Kremsner PG, Kublin JG, Lang T, Missinou MA, Mkandala C, Oduola AM, Premji Z, Robertson L, Sowunmi A, Ward SA, Winstanley PA.

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BACKGROUND: Increasing resistance to sulfadoxine-pyrimethamine is leading to a decline in its effectiveness. We aimed to assess the safety profile of chlorproguanil-dapsone (CD), and to compare the safety and efficacy of this drug with that of sulfadoxine-pyrimethamine (SP) as treatment for uncomplicated falciparum malaria. METHODS: We undertook a double-blind, randomised trial in 1850 consecutively recruited children with uncomplicated falciparum malaria, pooling data from five African countries. Analyses were based on all randomised patients with available data. FINDINGS: CD was significantly more efficacious than SP (odds ratio 3.1 [95% CI 2.0-4.8]); 1313 patients (96%) given CD and 306 (89%) given SP achieved acceptable clinical and parasitological response by day 14. Adverse events were reported in 46% and 50% of patients randomised to CD and SP, respectively (treatment difference -4.4%, [95% CI -10.1 to 1.3]). Haemoglobin in the CD group was significantly lower than in the SP group at day 7, a difference of -4 g/L (95% CI -6 to -2). Mean day 14 haemoglobin (measured only for the small number of patients whose day 7 data caused concern) was 94 g/L (92-96) and 97 g/L (92-102) after CD and SP, respectively. Glucose-6-phosphate dehydrogenase deficient patients on CD had greater odds than those on SP of having a fall of 20 g/dL or more in haemoglobin when baseline temperature was high. Methaemoglobinaemia was seen in the CD group (n=320, mean 0.4% [95% CI 0.4-0.4]) before treatment, 4.2% (95% CI 3.8-4.6) (n=301) at day 3, and 0.6% (0.6-0.7) (n=300) at day 7). INTERPRETATION: CD had greater efficacy than SP in Africa and was well tolerated. Haematological adverse effects were more common with CD than with SP and were reversible. CD is a useful alternative where SP is failing due to resistance.

Lancet. 2004 Jan 3;363(9402):18-22.

Dihydroartemisinin-piperaquine against multidrug-resistant Plasmodium falciparum malaria in Vietnam: randomised clinical trial.

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BACKGROUND: Southeast Asia has the most resistant malaria parasites in the world, which severely limits treatment options. There is general acceptance that to combat resistance, combinations of antimalarial drugs that include an artemisinin derivative should be used, and, if possible, these should be formulated in a single tablet. METHODS: We did a pilot randomised study in a tertiary referral hospital in Vietnam to compare the efficacy of 3-day regimens of dihydroartemisinin-trimethoprim-piperaquine (DHA-TP total dose 4.8/13.6/48 mg/kg, respectively) with the standard antimalarial regimen in Vietnam, artesunate-mefloquine (A3M total dose 12/25 mg/kg, respectively) in non-immune patients with uncomplicated Plasmodium falciparum malaria. 114 patients were randomised, 76 to DHA-TP and 38 to A3M. The subsequent open randomised trial at a Provincial Health Station compared DHA-TP, dihydroartemisinin-piperaquine, and A3M in 400 patients. In both studies all patients received directly observed therapy and were followed up for 56 days. The primary endpoint was reappearance of P falciparum malaria within 56 days of treatment. Analysis was by intention to treat. FINDINGS: The 56-day cure rate in the pilot study, adjusted for reinfections identified by PCR genotyping, was 97.4% (74/76) in the DHA-TP group and 100% (38/38) in the A3M group. In the second study, cure rates were similar in the three groups; DHA-TP 97.4% (153/157), dihydroartemisinin-piperaquine 98.7% (164/166), and A3M 98.7% (76/77). The DHA-TP and dihydroartemisinin-piperaquine regimens were well tolerated; fewer than 3% of patients had side-effects that might have been related to treatment, compared with 16% of A3M patients ($p<0.001$). No patients were lost to follow-up. INTERPRETATION: Dihydroartemisinin-piperaquine is an inexpensive, safe, highly efficacious fixed-dose antimalarial combination treatment that could make an important contribution to the control of multidrug-resistant falciparum malaria.

Trachoma

Lancet. 2004 Apr 3;363(9415):1093-8.

Role of flies and provision of latrines in trachoma control: cluster-randomised controlled trial.

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BACKGROUND: Eye-seeking flies have received much attention as possible trachoma vectors, but this remains unproved. We aimed to assess the role of eye-seeking flies as vectors of trachoma and to test provision of simple pit latrines, without additional health education, as

a sustainable method of fly control. METHODS: In a community-based, cluster-randomised controlled trial, we recruited seven sets of three village clusters and randomly assigned them to either an intervention group that received regular insecticide spraying or provision of pit latrines (without additional health education) to each household, or to a control group with no intervention. Our primary outcomes were fly-eye contact and prevalence of active trachoma. Frequency of child fly-eye contact was monitored fortnightly. Whole communities were screened for clinical signs of trachoma at baseline and after 6 months. Analysis was per protocol. FINDINGS: Of 7080 people recruited, 6087 (86%) were screened at follow-up. Baseline community prevalence of active trachoma was 6%. The number of Musca sorbens flies caught from children's eyes was reduced by 88% (95% CI 64-100; p<0.0001) by insecticide spraying and by 30% (7-52; p=0.04) by latrine provision by comparison with controls. Analysis of age-standardised trachoma prevalence rates at the cluster level (n=14) showed that spraying was associated with a mean reduction in trachoma prevalence of 56% (19-93; p=0.01) and 30% with latrines (-81 to 22; p=0.210) by comparison with the mean rate change in the controls. INTERPRETATION: Fly control with insecticide is effective at reducing the number of flies caught from children's eyes and is associated with substantially lower trachoma prevalence compared with controls. Such a finding is consistent with flies being important vectors of trachoma. Since latrine provision without health education was associated with a significant reduction in fly-eye contact by M sorbens, studies of their effect when combined with other trachoma control measures are warranted.

Helminth infection

Comment

Is the low prevalence of asthma in many developing countries related to the presence of intestinal helminths?

J Infect Dis. 2004 Mar 1;189(5):892-900. Epub 2004 Feb 18.

Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren.

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BACKGROUND: Several studies have shown an inverse association between helminth infections and atopy, but none have clearly established that the pathogens themselves, rather than other associated factors, cause the suppression of atopy. To show a direct link, prospective intervention studies are required. METHODS: A randomized, controlled trial was performed to study whether repeated anthelminthic treatment results in increased allergic sensitivity to house dust mites (HDMs) in chronically infected children. The trial population consisted of 317 Gabonese schoolchildren with a high prevalence of intestinal helminths. Intervention consisted of treatment every 3 months with praziquantel and mebendazole and with placebo in the control group. Follow-up lasted 30 months: at 6-month intervals, skin-test sensitivity to mites,

helminth infection status, and levels of total IgE were determined. RESULTS: Treatment resulted in a significant increase in the rate of developing skin sensitivity to HDMs (hazard ratio, 2.51; 95% confidence interval, 1.85-3.41), which was mediated, in part, by reductions in Ascaris and/or Trichuris infections. Levels of total IgE were reduced, but this did not mediate the effect of treatment on skin-test reactivity. CONCLUSIONS: Anthelminthic treatment of chronically infected children results in increased atopic reactivity, which indicates that helminths directly suppress allergic reactions.

Oral health

Comment

This year two RCTs from China show the importance of schools in public child health. School milk programs increase growth and bone density (see section on Nutrition) and brushing teeth at school improves oral health knowledge and behaviour.

J Dent Educ. 2004 Jan;68(1):50-4.

Evaluation of a fissure sealant program as part of community-based teaching and training.

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Since 1995 the Department of Community Dentistry of the University of Pretoria has been involved in the rendering of mobile primary oral health care services to children in the Hammanskraal area of Gauteng, South Africa, as part of their students' community-based training. Mokonyama Primary School was identified as the first school where a primary oral health care service could be rendered. The objective of this study was to evaluate the impact (outcomes) of a fissure sealant program on the dentition status of the school children. Seven years after the implementation of the program, the dentition status of children at Mokonyama was compared with that of a comparable group of children from the same area who were not exposed to the program. The results showed that the decayed, missing, and filled teeth in the primary dentition (dmft) in the six-year-old group in Mokonyama (1.74) did not differ significantly from the dmft (1.43) of the control group ($p = 0.49$). The decayed, missing, and filled teeth in the permanent dentition (DMFT) of 0.59 for the fifteen-year-old group in Mokonyama, however, differed significantly ($p = 0.0001$) from the DMFT of the control group (2.38). Fifteen-year-old children in Mokonyama had 75.2 percent fewer caries than their counterparts in the control group.

Community Dent Oral Epidemiol. 2003 Dec;31(6):412-6.

Effectiveness of an oral health education and caries prevention program in kindergartens in China.

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OBJECTIVES: To evaluate the effect of a 2-year oral health education and caries prevention program implemented in kindergartens in China. METHODS: Seven hundred and thirty-one 3-year-old children were recruited from 10 kindergartens in Miyun County, Beijing, China. The kindergartens were randomly divided into two groups. Oral health education was provided to teachers in the test kindergartens every 3 months. Oral health education sessions were conducted for the test children monthly and for their parents semiannually. Children in the test kindergarten brushed their teeth twice daily with fluoridated toothpaste (1100 ppm F-) in their kindergarten under the supervision of teachers during weekdays. No oral health education session and no supervised tooth brushing activities were carried out in the control kindergartens. A clinical examination of the study children and a questionnaire survey of their parents were conducted at baseline and after a 2-year program. RESULTS: Five hundred and fourteen children remained in the study after 2 years. The mean caries increments of the test group (n = 258) and the control group (n = 256) were 2.47 and 3.56 dmfs, respectively. The reduction in dmfs increment was 30.6% (P = 0.009). At the evaluation, a significantly higher percentage of children in the test group than in the control group reported brushing their teeth twice a day (87.6% vs. 69.0%; P < 0.001). Parents of children in the test group had better oral health knowledge and attitude than the parents of children in the control group. CONCLUSION: This oral health education program was effective in establishing good oral health habits among preschool children and in increasing oral health knowledge of their parents, in conjunction with supervised daily tooth brushing with fluoridated toothpaste, which could reduce the development of new dental caries in preschool children in China.

Hydrocephalus

S Afr Med J. 2003 Nov;93(11):865-8.

Visuospatial deficits in children 3-7 years old with shunted hydrocephalus.

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OBJECTIVE: To define non-verbal intelligence deficits in children 3-7 years of age following shunted hydrocephalus (HCP). DESIGN: Prospective randomised single-blinded study. Thirty shunted HCP (study) and 30 cardiac (control) patients between the ages of 3 and 7 years were compared on eight non-verbal subtests of the Junior South African Individual Scales (JSAIS). SETTING: Department of Neurosurgery at Wentworth Hospital, Durban, South Africa. RESULTS: Significant differences between the HCP and cardiac groups were recorded on all eight subtests of the JSAIS. The HCP group experienced problems with spatial orientation, perceptual planning and organisation, emotive deficits, abstract thinking and visual concepts.

CONCLUSION: All patients with shunted HCP had specific deficiencies in defined cognitive areas of non-verbal intelligence when compared with the controls. Further studies are warranted to determine the effects of ventriculoperitoneal shunting on non-verbal intelligence so that the special educational needs of HCP children may be met.

HIV

Comment

Reduction of the risk of vertical HIV transmission has been successfully achieved by using nevirapine as a single dose to the mother and a single dose to the newborn. This year RCTs have shown that the addition of zidovudine to the infant in the first week of life provides no additional benefit. One RCT showed that giving nevirapine daily to infants in the first 6 months of life was safe for the infant and achieved adequate drug levels, but whether this will reduce the risk of infection through breast feeding will require more research. Placental malaria may increase the risk of mother to child transmission of HIV.

Arch Dis Child. 2003 Dec;88(12):1112-8.

The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi.

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AIM: To compare presentation, progress, and outcome of acute bacterial meningitis in HIV seropositive and seronegative children. METHODS: A double blind randomised placebo controlled study of the use of dexamethasone as adjuvant therapy in acute bacterial meningitis, in children aged 2 months to 13 years, was carried out from July 1997 to March 2001. A total of 598 children were enrolled, of whom 459 were tested for HIV serostatus. RESULTS: Of the 459 children, 34% were HIV seropositive. Their presentation was similar to HIV seronegative children but more were shocked on arrival at hospital (33/157 v 12/302), and more had a focus of infection (85/157 v 57/302). HIV positive children had a higher incidence of Streptococcus pneumoniae infections (52% v 32%). Sixty four cases relapsed; 67% were in HIV positive patients. **The mortality in HIV positive children was 65% compared with 36% in HIV negative children.** The number of survivors in each group was similar. Hearing loss was more common in HIV negative than HIV positive children (66.3% v 47.2%). **Steroid therapy had no influence on meningitis in HIV positive children, but the mortality in HIV negative children was 61% in children given steroids, and 39% in those who did not receive steroids.** CONCLUSION: HIV seropositive children who develop bacterial meningitis have a high mortality and are prone to recurrent disease. There is an urgent need to prevent both primary and recurrent infections.

Trans R Soc Trop Med Hyg. 2003 Mar-Apr;97(2):212-6.

Subclinical mastitis among HIV-infected and uninfected Zimbabwean women participating in a multimicronutrient supplementation trial.

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Subclinical mastitis, defined as raised milk sodium/potassium (Na/K) ratio is common and associated with poor infant growth and increased mother-to-child HIV transmission. In 1996-97, we conducted a randomized controlled trial of multiple micronutrient supplementation, at recommended daily allowance levels, from 22 to 35 weeks gestation until 3 months post-partum, on the prevalence and severity of subclinical mastitis among 84 HIV-infected and 83 HIV-uninfected lactating Zimbabwean women and on their infants' growth. Spot milk samples collected before 4.5 months post-partum were analysed for Na/K ratio by flame photometry. There was no significant difference in prevalence of subclinical mastitis between HIV-infected and HIV-uninfected women. After controlling for infant age at time of sampling, micronutrient-supplemented HIV-infected women had non-significantly (P = 0.08) lower geometric mean Na/K ratio (0.43, 95% CI 0.35-0.51) than HIV-infected women given placebo (0.51, 95% CI 0.42-0.61). Micronutrient supplementation had no effect on the prevalence of subclinical mastitis among HIV-uninfected women (odds ratio [OR] = 1.26, 95% CI 0.45-3.51, P = 0.80) but induced a borderline decrease in prevalence (OR = 2.82, 95% CI 0.96-8.26, P = 0.07) among HIV-infected women. Infant weight between 1.5 and 4.5 months was lower in women with higher milk Na/K ratio. Thus, the importance of subclinical mastitis for infant growth suggests that further investigations to decrease the condition, perhaps using higher micronutrient doses, are warranted.

J Acquir Immune Defic Syndr. 2003 Dec 15;34(5):482-90.

Safety and trough concentrations of nevirapine prophylaxis given daily, twice weekly, or weekly in breast-feeding infants from birth to 6 months.

Shetty AK, Coovadia HM, Mirochnick MM, Maldonado Y, Mofenson LM, Eshleman SH, Fleming T, Emel L, George K, Katzenstein DA, Wells J, Maponga CC, Mwatha A, Jones SA, Abdool Karim SS, Bassett MT; HIVNET 023 Study Team.

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Despite the success of antiretroviral prophylaxis in reducing mother-to-child HIV-1 transmission, postpartum transmission through breast milk remains a problem. Antiretroviral administration to the infant during the period of breast-feeding could protect against postnatal transmission. An open-label phase 1/2 study was designed to assess the safety and trough concentrations of nevirapine (NVP) given once weekly (OW), twice weekly (TW), or once daily (OD) to HIV-exposed breast-feeding infants for 24 weeks. Following maternal dosing with 200 mg NVP orally at onset of labor, breast-feeding infants were randomized within 48

hours of birth to 1 of 3 regimens: arm 1, NVP given OW (4 mg/kg from birth to 14 days, upward arrow to 8 mg/kg from 15 days to 24 weeks), arm 2, NVP given TW (4 mg/kg from birth to 14 days, upward arrow to 8 mg/kg from 15 days to 24 weeks), and arm 3, NVP given OD (2 mg/kg from birth to 14 days, upward arrow to 4 mg/kg from 15 days to 24 weeks). Trough NVP concentrations and clinical and laboratory abnormalities were monitored. Of the 75 infants randomized (26 to OW, 25 to TW, and 24 to OD dosing), 63 completed the 32-week follow-up visit. No severe skin, hepatic, or renal toxicity related to NVP was observed. Neutropenia occurred in 8 infants. Trough NVP levels were lower than the therapeutic target (100 ng/mL) in 48 of 75 (64.0%) samples from infants in the OW arm, 3 of 65 (4.6%) samples in the TW arm, and 0 of 72 samples in the OD arm. Median (range) trough NVP concentrations were 64 ng/mL (range: <25-1519 ng/mL) with OW dosing; 459 (range: <25-1386 ng/mL) with TW dosing; and 1348 (range: 108-4843 ng/ml) with OD dosing. Our data indicate that NVP prophylaxis for 6 months was safe and well tolerated in infants. **OD NVP dosing resulted in all infants with trough concentration greater than the therapeutic target and maintenance of high drug concentrations.** A phase 3 study is planned to assess the efficacy of OD infant NVP regimen to prevent breast-feeding HIV-1 transmission.

JAMA. 2004 Jul 14;292(2):202-9.

Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial.

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CONTEXT: Antenatal counseling and human immunodeficiency virus (HIV) testing are not universal in Africa; thus, women often present in labor with unknown HIV status without receiving the HIVNET 012 nevirapine (NVP) regimen (a single oral dose of NVP to the mother at the start of labor and to the infant within 72 hours of birth). OBJECTIVE: To determine risk of mother-to-child transmission of HIV when either standard use of NVP alone or in combination with zidovudine (ZDV) was administered to infants of women tested at delivery. DESIGN, SETTING, AND PARTICIPANTS: A randomized, open-label, phase 3 trial conducted between April 1, 2000, and March 15, 2003, at 6 clinics in Blantyre, Malawi, Africa. The trial included all infants born to 894 women who were HIV positive, received NVP intrapartum, and were previously antiretroviral treatment-naive. Infants were randomly assigned to NVP (n = 448) and NVP plus ZDV (n = 446). Infants were enrolled at birth, observed at 6 to 8 weeks, and followed up through 3 to 18 months. The HIV status of 90% of all infants was established at 6 to 8 weeks. INTERVENTION: Mothers received a 200-mg single oral dose of NVP intrapartum and infants received either 2-mg/kg oral dose of NVP or NVP (same dose) plus 4 mg/kg of ZDV twice per day for a week. MAIN OUTCOME MEASURES: HIV infection of infant at birth and 6 to 8 weeks, and adverse events. RESULTS: **The mother-to-child transmission of HIV at birth was 8.1% (36/445) in infants administered NVP only and 10.1% (45/444) in those administered NVP plus ZDV (P =.30).** A life table estimate of transmission at 6 to 8 weeks was 14.1% (95% confidence interval [CI], 10.7%-17.4%) in infants who received NVP and 16.3% (95% CI, 12.7%-19.8%)

in those who received NVP plus ZDV (P =.36). For infants not infected at birth and retested at 6 to 8 weeks, transmission was 6.5% (23/353) in those who received NVP only and 6.9% (25/363) in those who received NVP plus ZDV (P =.88). Almost all infants (99%-100%) were breastfed at 1 week and 6 to 8 weeks. Grades 3 and 4 adverse events were comparable; 4.9% (22/448) and 5.4% (24/446) in infants receiving NVP only and NVP plus ZDV, respectively (P =.76). CONCLUSIONS: The frequency of mother-to-child HIV transmission at 6 to 8 weeks in our 2 study groups was comparable with that observed for other perinatal HIV intervention studies among breastfeeding women in Africa. The safety of the regimen containing neonatal ZDV was similar to that of a standard NVP regimen.

N Engl J Med. 2004 Jul 15;351(3):217-28. Epub 2004 Jul 09.

Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand.

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BACKGROUND: Although zidovudine prophylaxis decreases the rate of transmission of the human immunodeficiency virus (HIV) type 1 substantially, a large number of infants still become infected. We hypothesized that the administration, in addition to zidovudine, of a single dose of oral nevirapine to mothers during labor and to neonates would further reduce transmission of HIV. METHODS: We conducted a randomized, double-blind trial of three treatment regimens in Thai women who were receiving zidovudine therapy during the third trimester of pregnancy. In one group, mothers and infants received a single dose of nevirapine (nevirapine-nevirapine regimen); in another, mothers and infants received nevirapine and placebo, respectively (nevirapine-placebo regimen); and in the last, mothers and infants received placebo (placebo-placebo regimen). The infants also received one week of zidovudine therapy and were formula-fed. The end point of the study was infection with HIV in the infants, established by virologic testing. RESULTS: Between January 15, 2001, and February 28, 2003, a total of 1844 Thai women were enrolled. At the first interim analysis, the independent data monitoring committee stopped enrollment in the placebo-placebo group. Among women who delivered before the interim analysis, the as-randomized Kaplan-Meier estimates of the transmission rates were 1.1 percent (95 percent confidence interval, 0.3 to 2.2) in the nevirapine-nevirapine group and 6.3 percent (95 percent confidence interval, 3.8 to 8.9) in the placebo-placebo group (P<0.001). The final per-protocol transmission rate in the nevirapine-nevirapine group, 1.9 percent (95 percent confidence interval, 0.9 to 3.0), was not significantly inferior to the rate in the nevirapine-placebo group (2.8 percent; 95 percent confidence interval, 1.5 to 4.1). Nevirapine had an effect within subgroups defined by known risk factors such as viral load and CD4 count. No serious adverse effects were associated with nevirapine therapy. CONCLUSIONS: A single dose of nevirapine to the mother, with or without a dose of nevirapine to the infant, added to oral zidovudine prophylaxis starting at 28 weeks' gestation, is highly effective in reducing mother-to-child transmission of HIV.

AIDS. 2003 Nov 21;17(17):2539-41.

The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda.

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We examined the association of placental malaria and mother-to-child transmission (MTCT) of HIV in a prospective community-randomized trial in Rakai District, Uganda. In the 746 HIV-positive mother-infant pairs, the MTCT rate was 20.4%. Placental malaria was more common in HIV-positive than HIV-negative women. After multivariate adjustment for HIV viral load, the risk of MTCT associated with placental malaria was 2.89 and with HIV viral load the risk was 2.85. Interventions to prevent malaria during pregnancy could potentially reduce MTCT.

Public health

Eur J Clin Nutr. 2003 Dec;57(12):1562-8.

Water and sanitation associated with improved child growth.

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OBJECTIVE: To examine the relation between household water and sanitation, and the risk of stunting and reversal of stunting in Khartoum and Crezira regions, Sudan. DESIGN: Prospective cohort study. SETTING: A total of 25 483 children aged 6-72 months from rural Sudan enrolled in an 18-month field trial in 1988 to study the effect of vitamin A supplementation on child health and survival. RESULTS: The mean height-for-age z-scores at baseline and the end of study were -1.66 and -1.55, respectively, for the group with water and sanitation facilities, and -2.03 and -1.94 for the group without water and sanitation, after adjustment for age, region, gender, mother's literacy, intervention group (vitamin A vs placebo), family wealth, breastfeeding and cleanliness. Among children of normal height-for-age at baseline, the risk of stunting (<-2 height-for-age z-score) was lowest in the group that came from homes that had both water and sanitation compared to children from homes without these facilities (multivariate RR=0.79, 95% CI 0.69-0.90). Among children stunted at baseline, those coming from homes with water and sanitation had a 17% greater chance of reversing stunting than those coming from homes without either facility (adjusted RR=1.17, 95% CI 0.99-1.38). We did not detect a synergistic association between access to water and sanitation. CONCLUSIONS: Water and sanitation are independently associated with improved growth of children. SPONSORSHIP: None.

Vitamin A

Trop Med Int Health. 2003 Dec;8(12):1051-61.

Malaria parasitaemia in relation to HIV status and vitamin A supplementation among pre-school children.

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OBJECTIVES: To ascertain whether malaria parasitaemia in children is associated with HIV status. To examine the effect of vitamin A supplementation on malaria parasitaemia in children. METHODS: We studied the cross-sectional associations between HIV status and malaria parasitaemia among 546 children 6-60 months of age who participated in a double-blind, randomized clinical trial of vitamin A supplementation. Prevalence ratios and 95% confidence intervals (CI) were estimated for the presence of malaria parasites at baseline by HIV status in uni- and multivariate models that adjusted for sociodemographic and environmental variables. Among children with malaria, correlates of high parasite loads were identified. Next, we examined the effect of vitamin A supplementation on the risk of malaria parasitaemia and high parasite density at 4-8 months of the first dose in a subset of children. RESULTS: The prevalence of malaria parasitaemia was 11.4% among HIV-infected children, compared with 27.6% among uninfected. After adjusting for season, anaemia, use of bednets, maternal education and indicators of socioeconomic status, we found some evidence for lower prevalence of parasitaemia among HIV positive compared with HIV-negative children (prevalence ratio=0.56; 95% CI=0.29, 1.09; P=0.09). Other important correlates of malaria parasitaemia at baseline included low level of maternal education, poor quality of water supply, and the presence of animals at home. **Vitamin A supplementation did not have a significant effect on malaria parasitaemia at 4-8 months of follow-up, overall or within levels of potential effect modifiers.** CONCLUSION: **HIV infection appears to be negatively correlated with malaria parasitaemia in this group of children.** Investing in women's education is likely to decrease the prevalence of malaria parasitaemia in children. Vitamin A supplementation does not seem to have an effect on malaria parasitaemia in this population; possible benefits against clinical episodes and severe malaria deserve further examination.

Sand-fleas

Ann Trop Med Parasitol. 2003 Oct;97(7):743-9.

Topical treatment of tungiasis: a randomized, controlled trial.

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Tungiasis is caused by the penetration of the female sand flea Tunga penetrans into the epidermis of its host. Human infestation with this ectoparasite is hyper-endemic in many resource-poor communities in sub-Saharan Africa, the Caribbean and South America and is associated with considerable morbidity. Currently, there is no effective drug available to treat tungiasis (or at least none for which a parasiticidal effect has been clearly demonstrated). In an attempt to fill this gap, the effects of treatment with topical ivermectin (lotion), thiabendazole (ointment and lotion), metrifonate (lotion) or placebo lotion were compared in a randomized trial. A total of 108 subjects with 169 tungiasis-infested feet participated in the study. **The results show that topical ivermectin, metrifonate or thiabendazole can each significantly reduce the number of lesions caused by embedded sand fleas.** Further studies are needed to optimise the doses and administration of these compounds.

Ann Allergy Asthma Immunol. 2004 Apr;92(4):446-52.

Immune and histopathologic examination of flea bite-induced papular urticaria.

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BACKGROUND: Papular urticaria caused by flea bite presents clinical symptoms of hypersensitive reaction accompanied by skin lesions. Diagnostic and therapeutic approaches to the disease often go unrewarded, partly because of our incomplete understanding of the underlying immunopathogenesis. OBJECTIVE: To characterize the immune response to the flea bite in patients with papular urticaria. METHODS: This study included 45 randomly selected patients and 17 controls. Cutaneous allergy tests were performed. The histopathologic and immunohistochemical characteristics of cellular infiltrate in skin lesions were established. Immunoblot analysis was used to describe the specific characteristics of flea proteins recognized by IgE and IgG in patients' serum samples. RESULTS: Cutaneous allergy test results were negative in 87% to 98% of patients and in 88% to 100% of controls. Histopathologic and immunohistochemical studies revealed a predominance of eosinophils and CD4+ T lymphocytes. Immunoblotting did not show significant differences in IgG response between patients and controls. IgE recognition of flea proteins appears to decrease as the disease progresses. CONCLUSIONS: Our results suggest that the clinical manifestations of papular urticaria are mediated by a complex immune response involving more than one mechanism, with evidence forboth an IgE response and a cell-mediated type IV response.

Tuberculosis and BCG vaccine

Comment

A research team from West Africa provides further evidence this year of the non-specific effect of vaccines on child mortality. The good news is that BCG may reduce child mortality by a

minimum of 15%, greater than one would expect from an effect on the prevention of tuberculosis infection alone.

There may be substantial ascertainment bias in the study below from south India, if the subsequent diagnosis of tuberculosis is based partly on Mantoux reaction. In addition a large indurated reaction to PPD at entry probably represents latent tuberculosis, so it is not surprising that there would be a higher rate of subsequent diagnosis of tuberculosis in this group.

Int J Tuberc Lung Dis. 2003 Nov;7(11):1083-91.

Association of initial tuberculin sensitivity, age and sex with the incidence of tuberculosis in south India: a 15-year follow-up.

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OBJECTIVE: To determine the association of initial tuberculin sensitivity, age and sex with the development of tuberculosis. METHODS: **A 15-year follow-up of 280000 subjects in south India, where new cases of tuberculosis were detected mainly by periodic population surveys.** Life-table technique was employed to estimate tuberculosis incidence and disease risk in survivors. The independent effect of tuberculin sensitivity, sex and age at intake was determined using Cox's proportional hazard model. RESULTS: Taking subjects with reaction size 0-7 mm to 3 IU PPD-S as reference group, the adjusted relative risk (RR) for developing culture-positive tuberculosis was 1.1, 1.9, 2.9, 3.6 and 3.3 for those with indurations of 8-11, 12-15, 16-19, 20-24 and > or = 25 mm ($P < 0.01$). Considering subjects aged 0-4 years as reference group, the adjusted RR for the other groups increased from 1.7 to 10.8 ($P < 0.01$). Males had a substantially higher incidence (adjusted RR 3.0, $P < 0.001$). The risk of culture-positive tuberculosis over 15 years in survivors was 3.3% (5.0% in males and 1.6% in females), and increased substantially with tuberculin sensitivity at intake. In those with > or = 12 mm at intake, the approximate lifetime risk was 6.1% (8.6% in males and 3.1% in females). CONCLUSION: The incidence of tuberculosis increased steadily with tuberculin sensitivity to PPD-S and age at intake. Males had a significantly higher risk than females in every PPD-S group and the overall risk was three-fold higher.

Vaccine. 2003 Jun 20;21(21-22):2782-90.

BCG scar and positive tuberculin reaction associated with reduced child mortality in West Africa. A non-specific beneficial effect of BCG?

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Previous studies have suggested that the bacille Calmette-Guerin (BCG) vaccine may have a non-specific beneficial effect on childhood survival in areas with high mortality. We examined

whether BCG-vaccinated children with a BCG scar or a positive tuberculin reaction had better survival than children without such reactions. As part of an ongoing two-dose measles vaccine trial for which children were recruited at 6 months of age, we examined 1813 children for BCG scar at 6 months of age and 813 BCG-vaccinated children were skin-tested for delayed hypersensitivity to tuberculin, tetanus and diphtheria. **We found that BCG-vaccinated children with a BCG scar had significantly lower mortality compared with BCG scar-negative children, the mortality ratio in the first 12 months of follow-up being 0.41 (0.25-0.67). BCG-vaccinated children with a positive tuberculin test had a mortality ratio of 0.45 (0.24-0.85) compared with tuberculin negative children.** These results were unchanged by control for potential confounders or using different cut-off points for a tuberculin-positive response. Exclusion of dead children who had HIV antibodies did not modify the estimate (mortality rate (MR)=0.46 (0.23-0.94)). After censoring for tuberculosis (TB) exposure at home**, the mortality ratios for having a scar and being tuberculin-positive were 0.46 (0.27-0.79) or 0.42 (0.21-0.84), respectively.** Children positive to tetanus or diphtheria in the skin test had the same mortality as children not responding to these vaccine-related antigens. Thus, BCG scar and a positive tuberculin reaction were associated with better survival in early childhood in an area with high mortality. Since nothing similar was found for responders to diphtheria-tetanus-pertussis (DTP) vaccine, and the effect could not be explained by protection against tuberculosis, the effect of BCG vaccination could be due to non-specific immune-stimulation protecting against other infections.

Trop Med Int Health. 2004 May;9(5):559-65.

Direct observation of treatment for tuberculosis: a randomized controlled trial of community health workers versus family members.

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We implemented community-based direct observation of treatment, short course (DOTS), including a randomized controlled trial of direct observation either by community health workers (CHWs) or family members, under operational conditions in a region of Swaziland. There was a high death rate of 15%, due to the high HIV rates in the region. There was no significant difference in the cure and completion rate between direct observation of treatment by CHWs and family members [2% difference (95% CI -3% to 7%), exact P = 0.52]. A before-and-after comparison of outcomes demonstrated that the cure and treatment completion rate improved from a baseline of 27-67% following implementation of community-based DOTS. We conclude that community-based tuberculosis DOTS can improve successful outcomes of treatment. However, direct observation can be undertaken effectively using either daily family or CHW supervision. The choice of treatment supporter should be based on access, patient preference and availability of CHW resource.

Leprosy

Comment

The design phase of this important RCT is described.

Int J Lepr Other Mycobact Dis. 2004 Mar;72(1):8-15.

Design of the leprosy component of the Brazilian BCG revaccination trial for assessing BCG effectiveness against leprosy in school children.

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BACKGROUND: BCG vaccination confers protection against leprosy, and vaccination among household contacts has been recommended in Brazil. Nevertheless, vaccination of the entire community against leprosy is not advocated as leprosy has low incidence in most populations. Despite that, in Brazil, BCG vaccination is recommended among school children to prevent tuberculosis and this large scale vaccination may also affect the occurrence of leprosy, which led to investigations of its impact on leprosy in endemic areas of Brazil. OBJECTIVES: To estimate the effectiveness against leprosy of a dose of BCG vaccine given to school children in a population with a high coverage of neonatal BCG. Long term objectives are to compare the impact of vaccination among schoolchildren with the existing recommendation to vaccinate household contacts of leprosy. STUDY DESIGN: Cluster randomized controlled field trial with no placebo. STUDY POPULATION: Children aged 7 to 14 years attending state schools with high coverage of neonatal BCG. METHODS: 286 state schools in the city of Manaus, Brazil, were randomized to receive BCG or not. Identifying information was collected for 152,438 school children, of whom 72,980 are in intervention schools. BCG vaccination was given intradermically to children in schools allocated to vaccination. Follow-up relies on ascertainement of cases diagnosed at the health services and notified to the reference center for leprosy.

Filariasis

Comment

This study shows there is no increase in complications when albendazole is added to diethylcarbamazine, but there was no evidence of better efficacy at 12 months follow-up in patients treated with combination therapy than in patients treated with DEC alone.

Trans R Soc Trop Med Hyg. 2004 Apr;98(4):205-17.

Safety, tolerability, efficacy and plasma concentrations of diethylcarbamazine and albendazole co-administration in a field study in an area endemic for lymphatic filariasis in India.

Kshirsagar NA, Gogtay NJ, Garg BS, Deshmukh PR, Rajgor DD, Kadam VS, Kirodian BG, Ingole NS, Mehendale AM, Fleckenstein L, Karbwang J, Lazdins-Helds JK.

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Filariasis control programmes are moving towards a strategy of repeated single-dose mass treatment of endemic populations. **Using a combination, such as albendazole (ALB) to diethylcarbamazine (DEC) gives both macrofilaricidal and anti-helmintic activity.** However, the safety of the combination versus DEC alone should be established in field studies in large populations prior to incorporation into national programmes. **The present study compared the safety, tolerability, and efficacy of single doses of DEC 6 mg/kg + ALB placebo with DEC 6 mg/kg + ALB 400 mg in populations living in two filariasis endemic villages in the district of Wardha in western India.** The study was double blind, parallel group, and randomized. Safety and tolerability study were studied in males and females older than 5 years. **Safety was assessed by monitoring if adverse events (AEs) over 5 days affected daily acivities.** Subjects in the 2 treatment groups experienced insignificantly different effects on daily activities and the combination was shown to be safe. Efficacy was evaluated by microfilaraemia (Mf), immunochromatographic test (ICT) and ultrasonography (USG) at 0, 3, 6, and 12 months of follow up. The efficacy study enrolled 103 male patients (aged 18-50 years) in microfilariae positive, clinical disease and asymptomatic, amicrofilaremic groups. There was no significant difference in efficacy between groups at 12 months. Within the Mf positive group, significant differences were seen in microfilaraemia ($P < 0.001$) with both treatments, and in USG ($P < 0.001$ and $P < 0.004$ respectively), at 12 months. **The present field study has shown the combination of DEC + ALB to be as safe as the single drug DEC and thus the combination can be put in use in the national filariasis control programmes. Both drugs were adequately absorbed. The study at present does not provide evidence for the greater efficacy of the combination at 12 months follow up. While the safety of the combination has been ascertained, the incorporation or otherwise of ALB into national programmes for greater efficacy must await results of studies with longer follow up.**

Leishmaniasis

Comment

Similar to the findings of the RCT below, a Cochrane review of lipid soluble amphotericin B versus amphotericin B in cancer patients with neutropenia indicated that some lipid soluble formulations may be better drugs than conventional amph B, producing less nephrotoxicity. Management of visceral leishmaniasis in patients with renal impairment is a problem, but lipid soluble amphotericin is not affordable for the vast majority of settings that leishmaniasis is a problem. However a new drug has been developed by an Indian pharmaceutical company, in collaboration with WHO, the World Bank and UNDP. Miltefosine (Impavido®), has cured

95% of the patients with visceral leishmaniasis treated with it in clinical trials (Bull World Health Organ vol.80 Aug. 2002)

Decreasing efficacy of first-line antimonials has been reported this year: from Nepal rising failure rates with sodium stiboglunate (Trans R Soc Trop Med Hyg. 2003 May-Jun;97(3):350-4).

Interestingly zinc sulphate has been reported as an effective treatment for disseminated cutaneous leishmaniasis this year, in an RCT among adults in Iran where intra-lesional injections of zinc sulphate were used (Dermatology. 2004;209(1):46-9) and in case reports from Saudi Arabia where oral zinc was given to patients with disseminated cutaneous leishmaniasis (Saudi Med J. 2004 Jul;25(7):951-4). Yet another role for this amazing micronutrient, and perhaps another role for BCG adjuvant (see below)!

Clin Infect Dis. 2004 Feb 1;38(3):377-83. Epub 2004 Jan 13.

Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations.

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In Bihar, India, where visceral leishmaniasis is hyperendemic, amphotericin B deoxycholate is now first-line parenteral treatment. To test the efficacy of amphotericin B deoxycholate versus that of its lipid formulations, Indian patients were randomized to receive treatment with amphotericin B deoxycholate (1 mg/kg on alternate days for 30 days; n=51), liposomal amphotericin B (2 mg/kg per day for 5 days; n=51), or amphotericin B lipid complex (2 mg/kg per day for 5 days; n=51). Infusion-associated reactions were frequent and persistent in subjects treated with amphotericin B deoxycholate. The illness of 3 patients failed to respond to treatment, and 5 patients experienced relapse. Final cure rates were similar. Estimated total treatment costs for a 25-kg patient-417 dollars for amphotericin B deoxycholate, 872 dollars for liposomal amphotericin B, and 947 dollars for amphotericin B lipid complex-differed as a result of drug cost. Substantial reductions (approximately 60%) in the price of liposomal amphotericin B and amphotericin B lipid complex would make treatment costs comparable to that of amphotericin B deoxycholate, permitting administration of short-course regimens in India.

Ann Trop Med Parasitol. 2003 Oct;97(7):737-41.

The prevalences of Wuchereria bancrofti antigenaemia in communities given six rounds of treatment with diethylcarbamazine, ivermectin or placebo tablets.

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The ICT filariasis card test was used to determine the prevalences of Wuchereria bancrofti antigenaemia among villagers in India. Prior to the tests, those living in the 15 study villages had been treated six times, in six rounds of mass treatment (with 54%-75% coverage) spread over 6 years, with single doses of diethylcarbamazine (five villages), ivermectin (five villages) or placebo (five villages). The corresponding overall prevalences (and ranges) of filarial antigenaemia were 20.2% (13.7%-28.6%), 22.6% (15.3%-34.3%) and 25.9% (22.6%-29.3%), respectively. The overall prevalence of antigenaemia in the villages where diethylcarbamazine (DEC) had been distributed (but not that in the 'ivermectin' villages) was significantly lower than that recorded in the 'placebo' villages ($z = 2.56$; $P < 0.05$). The prevalences of antigenaemia among the villagers aged 1-5 years (18.9%, 15.6% and 22.4% in the DEC, ivermectin and placebo villages, respectively) did not differ significantly with treatment ($P > 0.05$). The results indicate that annual mass treatments based on DEC or ivermectin, with 54%-75% treatment coverage, may have only a limited effect on the prevalence of infection with adult W. bancrofti. The possible reasons for the antigenaemias observed are discussed.

Vaccine. 2004 Mar 12;22(9-10):1320-6.

Safety, immunogenecity, and efficacy of an autoclaved Leishmania amazonensis vaccine plus BCG adjuvant against New World cutaneous leishmaniasis.

Armijos RX, Weigel MM, Calvopina M, Hidalgo A, Cevallos W, Correa J.

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The safety, immunogenecity, and efficacy of two doses of an autoclaved-killed, whole cell Leishmania amazonensis vaccine (IFLA/BR/67/PH8) and BCG adjuvant (n = 750) against cutaneous leishmaniasis (CL) was compared with placebo (n = 756) in a randomized, placebo-controlled, blinded study. **Systemic and local side-effects were more frequent in the vaccine than placebo group. Leishmanin skin test (LST) conversion was greater in the vaccine than placebo group 2 months after the second vaccination dose (74.4% versus 14.7%; P = 0.000001). The 26-month incidence of confirmed CL (n = 25) was similar between the vaccine (2.0%) and placebo groups (2.0% versus 1.3%; P > 0.05). LST conversion was not associated with CL protection and the vaccine did not offer significant protection against CL infection caused by L. Viannia spp. compared to placebo**.

J Infect Dis. 2003 Jun 15;187(12):1959-61. Epub 2003 May 29.

Field trial of a vaccine against new world cutaneous leishmaniasis in an at-risk child population: how long does protection last?

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During 12 months of follow-up in a randomized double-blind controlled field study, a killed whole-promastigote vaccine cocktail plus bacille Calmette-Guerin (BCG) adjuvant significantly reduced the incidence of cutaneous leishmaniasis (CL) in Ecuadorian children, compared with BCG alone. To determine how much longer protection might continue, the study was reblinded to permit 48 additional months of follow-up. During months 13-18, CL incidence remained lower in the vaccine group, compared with that in the control group (5.9% vs. 13.8%; chi2=8.8; P=.003), with vaccine efficacy calculated at 56.5% (95% confidence interval, 18.7%-76.7%); however, during months 24-60, no significant between-group differences were detected. Periodic administration of boosters may be necessary to maintain whole-parasite-vaccine protection against New World CL.

Anaesthesia

Reg Anesth Pain Med. 2004 Jan-Feb;29(1):28-31.

Efficacy of three doses of ketamine with bupivacaine for caudal analgesia in pediatric inguinal herniotomy.

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BACKGROUND AND OBJECTIVES: Ketamine administered systemically is a potent analgesic at subanesthetic plasma concentrations. Addition of ketamine to bupivacaine for caudal epidural block significantly prolongs the duration of postoperative analgesia. The purpose of this prospective, randomized double-blind study is to identify the optimal dose of ketamine that produces the maximum duration of caudal analgesia with minimal adverse effects as an adjuvant to bupivacaine for caudal epidural block. METHODS: Sixty children, aged 6 months to 10 years, undergoing inguinal herniotomy were allocated randomly to receive 1 of 3 solutions for caudal epidural block. Group 1 received 0.75 mL/kg of bupivacaine 0.25% with preservative-free ketamine 0.25 mg/kg, group 2 received 0.75 mL/kg of bupivacaine 0.25% with ketamine 0.5 mg/kg, and group 3 received 0.75 mL/kg of bupivacaine 0.25% with ketamine 1 mg/kg. Postoperative pain was assessed using the All India Institute of Medical Sciences pain discomfort scale. Rescue analgesia in the form of pethidine 1 mg/kg intramuscularly was administered when this score exceeded 4. RESULTS: **The mean duration of caudal analgesia was 8.8 hours in group 1 compared with 22.1 hours in group 2 (P <.001) and 25.2 hours in group 3 (P <.001). Supplemental analgesia requirements with pethidine were significantly less in group 2 (4 subjects) and group 3 (no subject) when compared with group 1 (18 subjects).** There were no differences between the groups in the incidence of motor blockade, urinary retention, emesis, or sedation. Group 3 had a significantly higher incidence of behavioral side effects such as odd behavior, agitation, or restlessness than groups 1 and 2. CONCLUSIONS: **The optimal dose of ketamine in our study was 0.5 mg/kg added to 0.75 mL/kg bupivacaine 0.25% for caudal epidural block without an increase in side effects.**

Pediatr Emerg Care. 2004 Mar;20(3):162-5.

The value of capnography during sedation or sedation/analgesia in pediatric minor procedures.

Yldzdas D, Yapcoglu H, Ylmaz HL.

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OBJECTIVE: To measure changes in end-tidal carbon dioxide levels (ETco2) with different sedation/analgesia (midazolam, ketamine, ketamine plus midazolam, midazolam plus fentanyl, and propofol) during pediatric minor surgical procedures and to determine whether there were significant increases in ETco2 with different drugs. METHODS: We conducted a prospective, randomized, clinical trial of 126 children who needed sedation/analgesia in pediatric intensive care unit in a university hospital. Patients were randomly assigned to 1 of 5 treatment groups. Group K received only intravenous (IV) ketamine 1 mg/kg; group M, IV midazolam 0.15 mg/kg; group KM, IV ketamine 1 mg/kg plus IV midazolam 0.1 mg/kg; group MF, IV midazolam 0.1 mg/kg plus IV fentanyl 2 microg/kg; and group P, IV propofol 2 mg/kg. **Side stream, nasal cannula ETco2 tracings were recorded on a capnograph (Capnostat, Marquette).** Recordings began prior to the administration of medications and continued throughout the procedure until the patient was fully awake. The primary outcome variable was the difference between peak ETco2 before and during sedation/analgesia. This value was determined by scanning the records for the peak ETco2 averaged over 5 breaths before and after the administration of medications. RESULTS: There was neither any statistical difference between presedation/analgesia and postsedation/analgesia ETco2 levels in the 5 groups ($P > 0.05$) nor any difference in the first 3 groups between presedation/analgesia, sedation/analgesia, and postsedation/analgesia (K, M, and KM) ($P > 0.05$). In the midazolam plus fentanyl and propofol groups, mean ETco2 during sedation/analgesia was higher than the mean ETco2 during presedation/analgesia and postsedation/analgesia ($P < 0.05$). Twenty-one patients (16, 6%) had respiratory depression [hypercarbia (ETco2 > 50 mm Hg) or hypoxia (oxygen saturation > 90% for over 1 minute)], 21 patients (16, 6%) had hypercarbia, and 4 patients (3.2%) had both hypoxia and hypercarbia. One of 4 patients was in the MF group, and 3 were in the P group. Two subjects (8%) in the KM group, 7 (28%) in the MF group, and 13 (52%) in the P group had hypercarbia. CONCLUSIONS: This study demonstrated that propofol and midazolam-fentanyl produced a higher incidence of respiratory depression and higher mean ETco2 during sedation/analgesia than presedation and postsedation/analgesia. Capnography can serve as a useful monitoring tool in the evaluation of ventilation during sedation or sedation/analgesia in clinically stable children.

Envenomenation

Trans R Soc Trop Med Hyg. 2004 Jan;98(1):28-42.

Clinical trial of two antivenoms for the treatment of Bothrops and Lachesis bites in the north eastern Amazon region of Brazil.

Pardal PP, Souza SM, Monteiro MR, Fan HW, Cardoso JL, Franca FO, Tomy SC, Sano-Martins IS, de Sousa-e-Silva MC, Colombini M, Kodera NF, Moura-da-Silva AM, Cardoso DF, Velarde DT, Kamiguti AS, Theakston RD, Warrell DA.

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The efficacies of specific Bothrops atrox-Lachesis and standard Bothrops-Lachesis antivenoms were compared in the north eastern Amazon region of Brazil. The main aim was to investigate whether a specific antivenom raised against the venom of B. atrox, the most important Amazon snake species from a medical point of view, was necessary for the treatment of patients in this region. **Seventy-four patients with local and systemic effects of envenoming by Bothrops or Lachesis snakes were randomly allocated to receive either specific (n = 38) or standard (n = 36) antivenoms**. In 46 cases (24 in the standard antivenom group, 22 in the other) the snake was identified either by enzyme immunoassay or by examination of the dead snake, as B. atrox in 45, L. muta in one. Patients were similar in all clinical and epidemiological respects before treatment. Results indicated that **both antivenoms were equally effective in reversing all signs of envenoming detected both clinically and in the laboratory. Venom-induced haemostatic abnormalities were resolved within 24 h after the start of antivenom therapy in most patients.** The extent of local complications, such as local skin necrosis and secondary infection, was similar in both groups. There were no deaths. The **incidence of early anaphylactic reactions was 18% and 19%**, respectively for specific and standard antivenoms; none was life-threatening. Measurement of serum venom concentrations by enzyme immunoassay (EIA) confirmed that both antivenoms cleared venom antigenaemia effectively. EIA also revealed that one patient had been bitten by Lachesis muta, although the clinical features in this case were not distinctive.

Oncology

Comment

While the antibiotics used in these 2 RCTs from South America are infrequently available in most developing countries, the RCT of outpatient treatment for low risk children with fever and neutropenia is encouraging. Management of childhood cancer in many hospitals in developing countries is frequently made difficult because of inability to separate cancer patients from the other children, who invariably have infectious diseases. Suboptimal infection control practices and crowded hospital wards make outpatient management of neutropenic cancer patients an attractive option.

Braz J Infect Dis. 2003 Apr;7(2):111-20.

Evaluation of ticarcillin/clavulanic acid versus ceftriaxone plus amikacin for fever and neutropenia in pediatric patients with leukemia and lymphoma.

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BACKGROUND: The empirical use of antibiotic treatments is widely accepted as a means to treat cancer patients in chemotherapy who have fever and neutropenia. Intravenous monotherapy, with broad spectrum antibiotics, of patients with a high risk of complications is a possible alternative. METHODS: We conducted a prospective open-label, randomized study of patients with lymphoma or leukemia who had fever and neutropenia during chemotherapy. Patients received either monotherapy with ticarcillin/clavulanic acid (T) or ceftriaxone plus amikacin (C+A). RESULTS: Seventy patients who presented 136 episodes were evaluated, 68 in each arm of the study. The mean neutrophil counts at admission were 217cells/mm(3) (T) and 201cells/mm(3) (C+A). The mean duration of neutropenia was 8.7 days (T) and 7.6 days (C+A). Treatment was successful without the need for modifications in 71% of the episodes in the T group and 81% in the C+A group (p=0.23). Treatment was considered to have failed because of death in two episodes (3%) in the T group and three episodes (4%) in the C+A group, and because of a change in the drug applied in one episode in the T group and two episodes in the C+A group. Overall success was 96% (T) and 93% (C+A). Adverse events that occurred in group T were not related to the drugs used in this study. CONCLUSION: In pediatric and adolescent patients with leukemia or lymphoma, who presented with fever and neutropenia, during chemotherapy, ticarcillin/clavulanic acid was as successful as the combination of ceftriaxone plus amikacin. It should be considered an appropriate option for this group of patients at high risk for infections.

Cancer. 2003 Apr 1;97(7):1775-80.

Outpatient, sequential, parenteral-oral antibiotic therapy for lower risk febrile neutropenia in children with malignant disease: a single-center, randomized, controlled trial in Argentina.

Paganini H, Gomez S, Ruvinsky S, Zubizarreta P, Latella A, Fraquelli L, Iturres AS, Casimir L, Debbag R.

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BACKGROUND: Recent reports and previous randomized trials conducted at the authors' institution suggested that children with lower risk febrile neutropenic (LRFN) may benefit from substitution of oral antibiotic therapy for parenteral therapy. The objective of this study was to determine the efficacy of parenteral-oral outpatient therapy in the management of children with LRFN who were receiving treatment for malignant disease. METHODS: From August 2000 to April 2002, 135 children with a median age of 7.5 years (range, 1.6-15.8 years) who had a total of 177 episodes of LRFN were included in a prospective, randomized, single-institution trial. Children with LRFN received a single dose of ceftriaxone and amikacin and completed a risk-assessment work-up. All patients were discharged immediately and, at 24

hours, were allocated randomly to two groups: Group A (89 episodes) received oral ciprofloxacin, and Group B (88 episodes) received intravenous ceftriaxone. RESULTS: Most patients (61% in Group A and 51% in Group B) were receiving treatment for leukemia (P value not significant [NS]). Twenty-eight children (31%) in Group A and 22 children (25%) in Group B displayed unexplained fever (P value NS). No significant differences in sites of initial infection were found between the two groups. The median duration of neutropenia was 4.2 days and 4.7 days for Group A and Group B, respectively (P value NS); the median duration of fever was 2.3 days and 2.6 days, respectively (P value NS); and the median duration of antibiotic treatment was 4.5 days and 4.8 days, respectively (P value NS). **The overall results of the study were excellent. Only four treatment failures in Group A (5%) and 6 treatment failures in Group B (7%) were observed. These patients were readmitted to the hospital and did well with appropriate treatment.** CONCLUSIONS: In children with LRFN who are receiving treatment for malignant disease, outpatient oral ciprofloxacin after 24 hours of a single dose of intravenous ceftriaxone and amikacin was as safe and efficacious as parenteral ceftriaxone. Outpatient management and early antibiotic withdrawal were safe for both groups. DOI 10.1002/cncr.11251

Development issues and behavioural problems

Comment

It is sad that such studies need to be done as the RCT below from Korea. The multiple adverse effects of emotional neglect (including stunting, extreme psychological impairment and increased physical illnesses) have been known about for at least 100 years, and have recently been demonstrated among children from Romanian orphanages (JAMA 1992 Dec 23-30;268(24):3446-51). Caring and consistent human interaction is as necessary as calories for normal growth and development.

Res Nurs Health. 2003 Dec;26(6):424-33.

Multisensory intervention improves physical growth and illness rates in Korean orphaned newborn infants.

Kim TI, Shin YH, White-Traut RC.

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The purpose of this study was to evaluate the effectiveness of a multisensory intervention on the physical growth and health of Korean orphaned infants. Fifty-eight full-term infants were randomly assigned to a control (n = 28) or an experimental (n = 30) group within 14 days postbirth. In addition to receiving the routine orphanage care, **infants in the experimental group received 15 min of auditory (female voice), tactile (massage), and visual (eye-to-eye contact) stimulation twice a day, 5 days a week, for 4 weeks.** Compared to the control group, the experimental group had gained significantly more weight and had larger increases in length and head circumference after the 4-week intervention period and at 6 months of age. In addition, the experimental group had significantly fewer illnesses and clinic visits. These data demonstrate that multisensory intervention in conjunction with human/social contact may be effective in facilitating growth for newborn infants placed in orphanages. Copyright 2003 Wiley-Liss, Inc. Res Nurs Health 26:424-433, 2003

Fam Process. 2003 Winter;42(4):531-44.

An outcome evaluation of the implementation of the Triple P-Positive Parenting Program in Hong Kong.

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The present study evaluated the effectiveness of the Positive Parenting Program (Triple P) with a sample of Chinese parents of children with early onset conduct-related problems in Hong Kong. The participants consisted of 91 parents whose children attended maternal and child health centers and child assessment centers for service, and were between three to seven years old. Participants were randomly assigned to the intervention (TP) and a waitlist control group

(WL). There was no significant difference in pre-intervention measures between the two groups. However, at post intervention, participants in the TP group reported significantly lower levels of child behavior problems, lower dysfunctional parenting styles, and higher parent sense of competence, compared to the WL group. Implications of these findings for the use of Triple P with families of Chinese descent are discussed.

Dengue

Pediatr Infect Dis J. 2004 Feb;23(2):99-109.

Safety and immunogenicity of a three dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children.

Sabchareon A, Lang J, Chanthavanich P, Yoksan S, Forrat R, Attanath P, Sirivichayakul C, Pengsaa K, Pojjaroen-Anant C, Chambonneau L, Saluzzo JF, Bhamarapravati N.

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OBJECTIVE: The safety and immunogenicity of tetravalent live-attenuated dengue vaccines after a three dose vaccination series were evaluated in Thai children. METHOD: One hundred three healthy flavivirus-seronegative schoolchildren ages 5 to 12 years were randomized to receive either dengue vaccine containing 3, 2, 1 and 2 log10 of the 50% cell culture infective dose, respectively, of the live-attenuated dengue vaccine serotypes 1, 2, 3 and 4 per dose (F3212; n = 40) or 3, 3, 1 and 3 log10 of the 50% cell culture infective dose (F3313; n = 42) or purified Vero cell rabies vaccine (control group; n = 21) given in a two dose schedule (3 to 5 months apart). A third dose was administered 8 to 12 months after the second dose to 90 subjects. Safety and immunogenicity were evaluated within 28 days after each injection. RESULTS: No serious adverse event related to the vaccines occurred. Most children experienced mild to moderate fever, rash, headache and myalgia occurring within 12 days after Dose 1 and generally lasting 3 days or less. One subject in Group F3212 had a 1-week dengue-like fever. Reactogenicity was minimal after Doses 2 and 3. Transient mild variations in liver enzymes and hematologic indices were noted mainly after Dose 1. After the third dose 89% of the subjects in Group F3212 seroconverted (neutralizing antibody response, > or =10) to all four serotypes, and all children in Group F3313 seroconverted. CONCLUSION: This study demonstrates a moderate although improvable reactogenicity and high seroconversion rates against the four serotypes of dengue after a three dose schedule of tetravalent live-attenuated dengue vaccine in children.

Hepatitis A

J Trop Pediatr. 2003 Dec;49(6):333-9.

Immunogenicity and safety of two doses of a paediatric hepatitis A vaccine in thai children: comparison of three vaccination schedules.

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As fewer children in Thailand are exposed to hepatitis A virus (HAV) and so do not have seroprotective anti-HAV antibodies, they are becoming an important source of HAV transmission. A flexible HAV vaccination schedule would facilitate incorporation of the vaccine into existing immunization programmes, and we compared the immunogenicity and safety of three HAV immunization schedules. An open, randomized, clinical trial was carried out in which healthy children were given a primary dose of the inactivated hepatitis A vaccine, Avaxim 80 paediatric, with a booster dose 6, 12 or 18 months later. Anti-HAV geometric mean concentrations (GMC), seroconversion rates, and GMC ratios (GMCR) of the three schedules were compared and reactogenicity was evaluated. Seroconversion rates were above 98 per cent (per group) up to the booster. The three schedules were equivalent in terms of GMCRs, each eliciting a large booster effect. Local reactions were reported for fewer than 9 per cent of each group after dose one and less frequently after the booster dose. Injection site pain, gastrointestinal tract disorders and fever were the most commonly reported adverse events. No vaccine-related serious adverse events were reported. It was concluded that the hepatitis A vaccine, Avaxim 80 paediatric, is safe and immunogenic when given as a two-dose schedule to healthy seronegative children aged 5-10 years, with the second dose given at either 6, 12 or 18 months after the first.

Opthalmology

Comment

An excellent example of a critical evaluation of an appropriate training program for non-medical health care workers in a resource-poor setting with a large disease burden. Local integrated eye care workers could manage the surgery for trachomatous trichiasis as well as opthalmologists in Ethiopia.

Ophthalmology. 2004 Mar;111(3):578-84.

Surgery for trichiasis by ophthalmologists versus integrated eye care workers: a randomized trial.

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OBJECTIVE: To study the outcome of bilamellar tarsal rotation (BTR) trichiasis surgery performed by ophthalmologists versus that done by integrated eye care workers (IECWs). DESIGN: Randomized prospective interventional trial. PARTICIPANTS: **Nine hundred eighty-two patients with various degrees of trachomatous trichiasis in central Ethiopia.** METHODS: Trachomatous trichiasis patients in 3 woredas (districts) in central Ethiopia were

enrolled. Trichiasis severity was graded. Patients were randomly assigned to surgery by 2 ophthalmologists and 2 IECWs. **On the seventh day postoperatively, patients were evaluated for undercorrection or other complications. If trichiasis was present, it was considered a failure of surgery (technical failure), and patients were excluded from the follow-up study, but repeat surgery was performed.** Those patients with good correction at the seventh day were examined again on the third and sixth months. Further follow-up evaluation is planned for the first, second, and third years postoperatively. MAIN OUTCOME MEASURES: Recurrence rate, recurrence difference in the various grades, and difference between surgeries done by ophthalmic surgeons and those done by IECWs. RESULTS: In the third month of follow-up, it was possible to locate 713 (73.0%) of the operated patients. Eighty-one of 713 (11.4%) individuals and 94 of 1286 (5.4%) operated lids developed recurrent trichiasis in this period. There was a linear trend of recurrence with grading (severity) at baseline (chi(2) = 22.017, P<0.001), but there was no difference in recurrence by age (chi(2) =1.53, P = 0.9 at the third month; chi(2) = 1.43, P = 0.9 at the sixth month). There was also no difference with regard to gender (0.38 < odds ratio < 1.14, P = 0.1). **The recurrence observed in the group of individuals operated on by ophthalmologists at the 3-month follow-up was 47 (12.1%) lids, and the recurrence observed in the group operated on by the IECWs was 34 (9.9%) lids, with no statistically significant difference (chi(2) =1.38, P = 0.24, 95% confidence interval [CI], -18% to 74%).** At the 6-month follow-up, 43 (6.2%) persons had recurrence (95% CI, 4.4%-8%). There was no statistically significant difference between the 2 groups of surgeons at the 6-month point of follow-up examination (chi(2) = 4.46, P = 0.2). The overall recurrence was 124 (14.3%) lids within the first 6 months. CONCLUSION: Recurrent trichiasis is common, especially in cases where the degree of trichiasis is severe at baseline. This suggests that these patients may need surgical overcorrection to decrease the recurrence rate. **The outcome of BTR surgery done by IECWs is similar to that of the ophthalmic surgeons. Because of these findings, we recommend that training of IECWs in trichiasis surgery may help to ameliorate the effects of the eye care worker shortage in developing countries.**

Pertussis vaccine

Comment

The cost of acellular pertussis vaccine will preclude its use in most developing countries for the foreseeable future.

Vaccine. 2003 Oct 1;21(27-30):4194-200.

Reactogenicity and immunogenicity of reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTpa) administered as a booster to 4-6 year-old children primed with four doses of whole-cell pertussis vaccine.

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A trial to compare the reactogenicity and immunogenicity of a reduced antigen content diphtheria-tetanus-acellular pertussis (dTpa) vaccine with diphtheria-tetanus-whole-cell pertussis (DTPw) vaccine was conducted in Thailand. **Three hundred and thirty children aged 4-6 years, primed with four doses of DTPw, received a single injection of either dTpa or DTPw. There was a significantly lower incidence of local and general reactions following dTpa than DTPw (P<0.001). One month after vaccination, 99.4 and 100% of all subjects had protective anti-diphtheria and -tetanus titers, respectively.** The vaccine response rate to pertussis antigens was similar in both groups, with 96.9% versus 92.5% for anti-pertussis toxin (PT), 96.9% versus 97.5% for anti-filamentous hemagglutinin (FHA) and 95.1% versus 90.8% for anti-pertactin (PRN) in the dTpa and DTPw groups, respectively. For anti-BPT, the vaccine response in the dTpa group was 29.6% versus 94.4% for DTPw. In conclusion, the dTpa vaccine was as immunogenic and significantly better tolerated than DTPw. The new dTpa vaccine could improve coverage for routine booster vaccination in children and provide a good replacement for DTP vaccines at 4-6 years of age.