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The value of nutritional support in selected infectious disease conditions: evidence from randomized controlled trials.

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Table 1: Effects of micronutrients and probiotics on malaria, tuberculosis and HIV infections

Disease condition		Malaria		Tuberculosis		HIV	
Nutrient (target group)	Effect (a)	No. of studies	References (b)	No. of studies	References (b)	No. of studies	References (b)
Vitamin A (adults)	+	0		0		1	123
	■	0		0		5	123 – 127
	▼	0		0		0	
Vitamin A (children)	+	3	22, 23, 24	1	118	1	127
	■	3	25, 26, 27	0		0	
	▼	0		0		0	
Vitamin A (pregnant/lactating)	+	0		0		0	
	■	0		0		2 (d)	128, 129
	▼	0		0		2 (d)	130, 131
Vitamin A + zinc	+	0		1	119	0	
	■	0		0		0	
	▼	0		0		0	
Zinc (children)	+	1	1	1	115	0	
	■	2	2, 3	0		0	
	▼	0		0		0	
Zinc (pregnant/lactating)	+	0		0		0	
	■	0		0		0	
	▼	0		0		1 (d)	133
Folic acid (children)	+	0		0		0	
	■	2	11, 28	0		0	
	▼	1	11	0		0	
Folic acid (pregnant/lactating)	+	1	20	0		0	
	■	0		0		0	
	▼	0		0		0	
Folic acid + iron (pregnant/lactating)	+	1	30	0		0	
	■	0		0		0	
	▼	0		0		0	
Vitamin B6 (children)	+	0		0		0	
	■	0		1	120	0	
	▼	0		0		0	
Vitamin D (children)	+	0		1	121	0	
	■	0		0		0	
	▼	0		0		0	
Vitamin C + vitamin E (adults)	+	0		0		1	132
	■	0		0		0	
	▼	0		0		0	
Iron (adults)	+	0		1	116	0	
	■	0		0		1	137
	▼	0		0		0	
Iron (children)	+	12	4 – 15	0		0	
	■ (c)	11	8 – 18	0		0	
	▼	1	13	0		0	
Iron (pregnant/lactating)	+	2	20, 21	0		0	
	■ (c)	1	21	0		0	
	▼	1	19	0		0	
Selenium (adults)	+	0		0		3	134 – 136
	■	0		0		2	134, 135
	▼	0		0		0	
Vitamin B1, B2, C + iron (children)	+	1	29	0		0	
	■	1	29	0		0	
	▼	0		0		0	

Disease condition		Malaria		Tuberculosis		HIV	
Nutrient (target group)	Effect (a)	No. of studies	References (b)	No. of studies	References (b)	No. of studies	References (b)
Vitamin A, D, E, C, B1, B2, niacin + iron (children)	+	1	31	0		0	
	■	1	31	0		0	
	▼	0		0		0	
Multivitamins + minerals (adults)	+	0		1	117	3	130, 147, 148
	■	0		0		1	147
	▼	0		0		1	147
Multivitamins + minerals (pregnant/lactating)	+	0		0		9 (d)	128, 131, 138 – 144
	■	0		0			
	▼	0		0			
Probiotics	+	0		1	122	0	
	■	0		0		0	
	▼	0		0		0	

Table 2: Effects of micronutrients and probiotics on helminths, cholera and other diarrheal conditions

Disease condition		Helminths		Cholera (e)		Other diarrhea	
Nutrient	Effect (a)	No. of studies	References (b)	No. of studies	References (b)	No. of studies	References (b)
Vitamin A	+	3	32, 33, 34	1	37	7	43 – 49
	■	1	32	0		13	42, 44, 47, 49 – 58
	▼	0		0		3	45, 46, 47, 59
Iron	+	2	35, 36	0		2	77, 80
	■	0		0		1	81
	▼	0		0		3	80, 81, 82
Zinc	+	0		3	38, 39, 40	17	40, 55, 56, 60 – 77
	■	0		1	41	8	51, 63, 65, 68, 69, 71, 72, 78
	▼	0		0		1	78
Folic acid	+	0		0		0	
	■	0		0		1	79
	▼	0		0		0	
Nicotinic acid	+	0		1		1	41
	■	0		0		0	
	▼	0		0		0	
Multiple micronutrients	+	0		0		0	
	■	0		0		0	
	▼	0		0		2	70, 77
Probiotics	+	0		0		23	83 – 106
	■	0		0		10	89, 104, 107 – 114
	▼	0		0		0	

Notes

(a) The effect is shown as:

- +
 -
 - ▼
- when the study provided statistically significant evidence for a positive/preventive role either in terms of being able to improve the micronutrient status or the clinical condition of the individuals tested;
- when the study provided no statistically significant evidence for any role;
- when the study provided statistically significant evidence for a negative/disease promoting role.

(b) The numbers refer to the papers listed in the bibliography. The main findings from each paper are summarized after the bibliographic data.

(c) Conflicting evidence exists on the possible role of iron supplements in the predisposition to malaria infection or the enhancement of its clinical severity. A lack of effect is therefore a positive outcome for iron supplementation with regard to indices of the disease.

(d) Although supplementation of pregnant women might have had no direct effect on the subjects own health, it might have affected the pregnancy outcome, the nutritional status of the baby and/or mother-to-child transmission.

(e) Studies were included if the authors of the paper used “cholera” as a keyword for the publication.

Introduction

At the UN General Assembly in September 2000 the heads of State and Government of all 191 member states adopted the United Nations Millennium Declaration. The Millennium Development Goals (MDGs) derived from this declaration are the world's time-bound and quantified targets for addressing extreme poverty in its many dimensions—income poverty, hunger, disease, lack of adequate shelter, and exclusion—while promoting gender equality, education, and environmental sustainability. They are also basic human rights—the rights of each person on the planet to health, education, shelter and security.

- Goal 1: Eradicate extreme poverty and hunger
- Goal 2: Achieve universal primary education
- Goal 3: Promote gender equality & empower women
- Goal 4: Reduce child mortality
- Goal 5: Improve maternal health
- Goal 6: Combat HIV/AIDS, malaria & other diseases
- Goal 7: Ensure environmental sustainability
- Goal 8: Develop a global partnership for development

In September 2005—five years after adoption of the Millennium Declaration and ten years before the Goals' deadlines—world leaders again met at the United Nations in New York to assess how far their pledges have been fulfilled, and to decide on what further steps are needed. It was reconfirmed that the elimination of malnutrition plays a central role in efforts to achieve six of the eight Millennium Development Goals.

Millennium Development Goal 6 pledges:

- to halt by 2015 and begin to reverse the spread of HIV/AIDS
- to halt by 2015 and begin to reverse the incidence of malaria and other major diseases.

Malnutrition may increase risk of HIV transmission, compromise antiretroviral therapy, and hasten the onset of full-blown AIDS and premature death. It increases the chances of tuberculosis infection, resulting in disease, and it also reduces malaria survival rates.

In 2005, AIDS had become the leading cause of premature death in sub-Saharan Africa and the fourth largest killer worldwide. In the European countries of the Commonwealth of Independent States (CIS) and parts of Asia, HIV is spreading at an alarming rate. Though new drug treatments prolong life, there is still no cure for AIDS, and prevention efforts must be intensified in every region of the world if the target is to be reached.

Malaria and tuberculosis together kill nearly as many people each year as AIDS, and represent a severe drain on national economies. Ninety per cent of malaria deaths occur in sub-Saharan Africa, where prevention and treatment efforts are being scaled up. Tuberculosis is on the rise, partly as a result of HIV/AIDS, though a new international protocol to detect and treat the disease is showing promise (Sources: The Millennium Development Goals Report 2005 and 'Repositioning Nutrition as Central to Development', the World Bank 2006).

A tool for efficient nutrition support

This publication summarizes the evidence available regarding the value of specific micronutrients and probiotics in the prevention and management of selected infectious disease conditions, and helps those responsible for achieving MDG6 to choose the most efficient and cost-effective solution.

About the tables

The tables presented here provide a simple matrix based on the peer reviewed scientific literature that describes the current state of knowledge from randomized controlled trials in humans as regards the effects of micronutrients and probiotics on malaria, tuberculosis, helminths, cholera and HIV infections. The document was compiled using the Medline scientific journal database. MESH terms and related articles were used in addition to hand searching of bibliographies of articles.

This was not a systematic review on the topic, and key publications may have been missed due to inadequate indexing in the database. The data are presented as simply as possible. As a result, some of the detail that is important when reviewing the strength of evidence (in particular, issues such as study design, dosage, duration, statistical power, quality of the publication, etc) might have been lost. Users of this document are therefore urged to refer to the original publication to ensure that the evidence is reported accurately.

The key question that was asked when reviewing papers was "Is there a role for nutrient X to play in condition Y?" The task is often extremely complex due to the fact that many infections are both the cause and consequence of undernutrition. In addition, it often happens that a study could find a positive effect on one outcome and no effect on another, for example a positive effect on micronutrient status and no effect on the clinical outcome. In such cases, studies were categorized as showing both positive and no effects.

To ensure that a wide spectrum of papers is covered, the authors kept the key question fairly broad. In cases where there is significant agreement amongst experts, such policy statements or position papers were used to support the published evidence. Systematic reviews and meta analyses were also utilized where possible and appropriate. – ■

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Zinc supplementation (10 mg elemental zinc for 6 days/week for 46 weeks) in children (6–60 months) living in a malaria-endemic area reduced morbidity due to Plasmodium falciparum. Zinc supplementation resulted in a 38% (95% CI 3–60, P = 0.037) reduction in Plasmodium falciparum health center-based episodes, defined as parasitemia > or = 9200 parasites/microl with axial temperature > or = 37.5°C or reported fever. Episodes accompanied by any parasitemia were also reduced by 38% (95% CI 5–60, P = 0.028), and episodes with parasitemia > or = 100,000/microl were reduced by 69% (95% CI 25–87, P = 0.009).

2. Zinc Against Plasmodium Study Group. Effect of zinc on the treatment of *Plasmodium falciparum* malaria in children: a randomized controlled trial. *Am J Clin Nutr* 2002; 76: 805–12.
Zinc supplementation (20 mg/d for infants, 40 mg/d for older children) for 4 days did not appear to provide a beneficial effect in the treatment of acute, uncomplicated falciparum malaria in preschool children compared to placebo treatment.

3. Muller O, Becher H, van Zweeden AB et al. Effect of zinc supplementation on malaria and other causes of morbidity in west African children: randomised double blind placebo controlled trial. *Brit Med J* 2001; 322: 1567.
Zinc supplementation (12.5 mg zinc sulphate/d) for 6 days/wk for 6 months had no effect on morbidity from falciparum malaria in children living in a malaria-endemic area, but it does reduce morbidity associated with diarrhoea.

4. Menendez C, Schellenberg D, Quinto L et al. The effects of short-term iron supplementation on iron status in infants in malaria-endemic areas. *Am J Trop Med Hyg* 2004; 71: 434–440.
Iron supplementation (2 mg/kg/day) between the ages of 2–6 months improved iron status at least up to 12 months of age in infants exposed to Plasmodium falciparum malaria.

5. Desai MR, Dhar R, Rosen DH et al. Daily iron supplementation is more efficacious than twice weekly iron supplementation for the treatment of childhood anemia in western Kenya. *J Nutr* 2004; 134: 1167–1174.
In a malaria-endemic area and after initial antimalarial treatment, 6 weeks of daily iron supplementation resulted in better hematological responses than twice weekly iron supplementation in the treatment of anemia in preschool children, regardless of whether adherence can be ensured (supervised vs unsupervised supplementation).

6. Terlouw DJ, Desai MR, Wannemuehler KA et al. Relation between the response to iron supplementation and sickle cell hemoglobin phenotype in preschool children in western Kenya. *Am J Clin Nutr* 2004; 79: 466–472.
Iron supplementation of children with mild anemia living in an area with widespread use of intermittent (at 4 and 8 wk) preventive treatment (IPT) with sulfadoxine pyrimethamine was efficacious compared to placebo treatment in increasing hemoglobin concentrations regardless of a child's HbS. The benefits of iron supplementation are likely to outweigh possible risks associated with malaria in children with the HbAA or HbAS phenotype.

7. Massaga JJ, Kitua AY, Lemnge MM et al. Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *Lancet* 2003; 361: 1853–1860.
Infants aged 12–16 weeks receiving iron supplementation were partly protected against anemia (protective efficacy 59.8%; 95% CI, 23.4–78.9), but not against malarial fevers compared to placebo treatment.

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Supplementation with iron in anemic children, aged 2–36 months, living in an area with intense malaria transmission resulted in a greater mean hemoglobin concentration of 0.79 g/dL (95% CI, 0.46–1.10 g/dL) at 12 weeks, compared with the placebo group. Iron supplementation did not affect the incidence of malaria parasitemia and clinic visits.

9. Verhoef H, West CE, Nzyuko SM et al. Intermittent administration of iron and sulfadoxine-pyrimethamine to control anaemia in Kenyan children: a randomised controlled trial. *Lancet* 2002; 360: 908–914.
Iron supplementation in anemic children living in areas of seasonal malaria transmission resulted in higher hemoglobin concentrations (10.7 g/L [7.1 to 14.3]) compared with the placebo group after 12 weeks. Survival analysis showed no evidence of substantially increased risk of malaria after iron supplementation.

10. Berger J, Dyck JL, Galan P et al. Effect of daily iron supplementation on iron status, cell-mediated immunity, and incidence of infections in 6–36 month old Togolese children. *Eur J Clin Nutr* 2000; 54: 29–35.
Iron supplementation (2–3 mg elemental iron per kg body weight) in children living in an environment where iron deficiency, malaria and other infections are frequent had a significant and positive effect on iron status of children and no impact on the incidence of infections, especially malaria compared to placebo treatment.

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- Supplementation with iron improved hematological recovery (differences in mean hemoglobin level after one month and at dry season follow-up = 0.70 g/dL, $P = 0.006$, and 0.81 g/dL, $P = 0.001$, respectively). Iron supplementation was not associated with increased prevalence of malaria. Supplementation with folic acid did not improve the hematological response but, among children who received pyrimethamine-sulfadoxine (Fansidar), the treatment failure rate was significantly higher among those given folic acid than among those given placebo.
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No significant differences were seen between placebo and iron supplementation in children (6 mo – 3 yr). However, children who received iron supplementation and who were free of malaria infection at the end of the trial showed improvement of their hematological status when compared to children receiving placebo and also free of malaria infection.
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Iron supplementation in children aged between 6 months and 5 years with iron-deficiency anemia during the rainy season when malaria transmission is maximal resulted in improved hematological and iron measurements compared to placebo treatment. However, fever associated with severe malarial parasitemia was significantly increased with iron supplementation.
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14. Harvey PW, Heywood PF, Nesheim MC et al. The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *Am J Trop Med Hyg* 1989; 40: 12–18.
Prepubescent schoolchildren in malaria endemic areas received either 200 mg ferrous sulfate or a placebo twice daily for 16 weeks. Iron status was significantly improved by the treatment. The treatment did not significantly affect parasite rate, parasite density, or levels of anti-malarial IgG. No changes in spleen size were observed in either group. These results suggest that, in malaria endemic areas, oral treatment for iron deficiency can be carried out in semi-immune or immune schoolchildren without adverse consequences
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Iron supplementation in children (6–36 months) did not affect the susceptibility to malaria nor the organism's response.
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Iron supplementation in children with severe malaria-associated anemia did not have any effect on the rate of parasitemia and on parasite density during 12 weeks of follow-up and did not affect hemoglobin concentrations after 12 weeks of treatment. This study provides no evidence to support routine iron supplementation to these children.
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Children aged 5 months to 3 years living in a malaria-endemic area received a low-dose micronutrient supplement (vitamin A, D, E, C, B1, B2, B6, niacin, iron) three times per week for 5 months. Micronutrient supplementation improved childhood anemia but did not affect malaria incidence.
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43. Barreto ML, Santos LM, Assis AM et al. Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 1994; 344: 228–231. *The overall incidence of diarrhea episodes was significantly lower in the vitamin-A-supplemented group than in the placebo group.*
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44. Sempertegui F, Estrella B, Camaniero V et al. The beneficial effects of weekly low-dose vitamin A supplementation on acute lower respiratory infections and diarrhea in Ecuadorian children. *Pediatrics* 1999; 104: e1. *Acute diarrheal disease and acute respiratory infection did not differ globally or by severity between supplement-treated*
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- and placebo groups. The risk of severe diarrhea was lower in supplement-treated children 18 to 23 months of age than in children on placebo in this age group but not in other age groups.*
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45. Donnen P, Dramaix M, Brasseur D et al. Randomized placebo-controlled clinical trial of the effect of a single high dose or daily low doses of vitamin A on the morbidity of hospitalized, malnourished children. *Am J Clin Nutr* 1998; 68: 1254–1260. *High-dose vitamin A supplementation had no significant effect on the duration of moderate or severe diarrhea. Children in the high-dose group with no edema had an increased risk of severe nosocomial diarrhea (relative risk: 2.42; 95% CI: 1.15, 5.11). Low-dose vitamin A supplementation significantly reduced the incidence of severe diarrhea in severely malnourished children (relative risk: 0.21; 95% CI: 0.07, 0.62) but showed no significant effect on the duration of moderate or severe diarrhea. Supplementation with high doses of vitamin A did not reduce morbidity in this population of malnourished and subclinically vitamin A-deficient children; daily, low doses appeared more beneficial for severely malnourished children*
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46. Fawzi WW, Mbise R, Spiegelman D et al. Vitamin A supplements and diarrheal and respiratory tract infections among children in Dar es Salaam, Tanzania. *J Pediatr* 2000; 137: 660–667. *Relative to those receiving placebo, children receiving vitamin A had a significantly smaller risk of severe watery diarrhea. Vitamin A supplementation was also associated with increased risk of acute diarrhea among normally nourished children or children with stunted growth but was relatively protective among children with wasting disease. Supplements may also have serious non-lethal adverse outcomes in well-nourished individuals.*
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47. Dibley MJ, Sadjimin T, Kjolhede CL, Moulton LH. Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 1996; 126: 434–442. *There was no overall effect of high-dose vitamin A supplements on the incidence of diarrheal disease (rate ratio 1.06, 95% confidence interval 0.920–1.225). However, the authors found a significant interaction between supplementation and age: vitamin A increased the incidence of diarrhea in children < 30 mo of age, but tended to reduce the incidence in older children.*
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Possible beneficial effects of a single oral dose of vitamin A supplementation on the incidence of diarrhea could not be demonstrated in the present study but the average duration of diarrhea per episode (2.1 vs. 3 days) differed between the experimental and control groups.

Zinc supplementation was associated with a reduced duration of diarrhea (13%, $p = 0.03$) and markedly reduced rate (43%, $p = 0.017$) of prolonged diarrhea (>7 days). Vitamin A supplementation was associated with a nonsignificant trend for reduced rate of prolonged diarrhea ($p = 0.089$).

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The study results indicate that vitamin A supplements did not produce a substantial reduction in the prevalence rates of diarrhea, in spite of a reported reduction in all-cause mortality.
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Supplementation with zinc, vitamin A, or combined zinc and vitamin A had no significant effect on duration of diarrhea or rate of readmission compared with placebo. This finding may not apply to children with malnutrition, for whom other studies suggest a benefit.
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Diarrhea morbidity was similar in the vitamin A and placebo groups.
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Weekly treatment with the low-dose vitamin A supplement did not influence the incidence, severity, or duration of diarrhea.
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54. Rollins NC, Filteau SM, Elson I, Tomkins AM. Vitamin A supplementation of South African children with severe diarrhea: optimum timing for improving biochemical and clinical recovery and subsequent vitamin A status. *Pediatr Infect Dis J* 2000; 19: 284–289.
Vitamin A did not significantly improve early clinical or biochemical recovery from severe diarrhea.
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The results indicate that supplementation with zinc, but not with vitamin A, in persistent diarrhea reduces stool output, prevents weight loss and promotes earlier recovery.
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Zinc supplementation was associated with a reduced duration of diarrhea (13%, $p = 0.03$) and markedly reduced rate (43%, $p = 0.017$) of prolonged diarrhea (>7 days). Vitamin A supplementation was associated with a nonsignificant trend for reduced rate of prolonged diarrhea ($p = 0.089$).
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The incidence of diarrhoea was similar in the vitamin A supplementation and placebo groups.
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The study shows an increased 2-week prevalence of diarrhea after vitamin A supplementation
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There was a marked reduction in the duration of diarrhea (1.1 vs 2.6 days) and of watery stools in the zinc-supplemented group.
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Zinc given daily substantially reduced the duration of diarrhea. The effect of zinc was not dependent on or enhanced by concomitant vitamin A administration but increased vomiting due to zinc administration could be a problem
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Zinc supplementation had no effect in children 6–11 months old. In children aged >11 months there was significantly less diarrhea in the zinc group. In boys >11 months old, supplementation resulted in a 26% (95% CI: 13%, 38%) lower diarrheal incidence and a 35% (95% CI: 20%, 50%) lower prevalence. In zinc-supplemented girls >11 months of age, the incidence was 17% (95% CI: 2%, 30%) lower and the prevalence was 19% (95% CI: 4%, 47%) lower. Overall, zinc supplementation resulted in a 17% (95% CI: 1%, 30%) lower diarrheal

incidence in children with plasma zinc concentrations $<9.18 \mu\text{mol/L}$ at enrollment and a 33% (95% CI: 6%, 52%) lower incidence in children with concentrations $<50 \mu\text{mol/L}$.

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Zinc supplementation had a significant impact on the incidence of persistent diarrhea only in children >1 year old and in children with low plasma zinc.
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Zinc supplementation in malnourished children with acute diarrhea may reduce the severity and duration of diarrhea, especially in children with low zinc levels.
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These results suggest that a short course of zinc supplementation to malnourished children during acute diarrhea reduces diarrheal morbidity during subsequent two months.
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The median incidence of diarrhea among children who received zinc supplementation was reduced by 22%. Zinc supplementation also produced a 67% reduction in the percentage of children who had one or more episodes of persistent diarrhea. No significant effects were found on the episodic prevalence of diarrhea, the number of days per episode, or the episodic prevalence.
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Oral zinc administration in acute diarrhea may shorten the diarrheal duration and frequency in children with relatively severe zinc depletion but not in those with adequate zinc status.
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The zinc group had fewer episodes of diarrhea than did the zinc+vitamins group. Morbidity was greater after supplementation with zinc plus multivitamins and minerals than it was after supplementation with zinc alone.
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The study reports a significant reduction in the duration of persistent diarrhea in selected subgroups of zinc-supplemented patients and not in the whole group.
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Supplementation (5 mg Zn) was associated with a 28% reduction in diarrhea prevalence over the 6-month period. There was no effect on any outcome with 1 mg zinc.
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Zinc supplementation reduced morbidity associated with diarrhea.
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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 authors claim that the effects are large enough to merit routine use of zinc during acute diarrhea in developing countries.
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76. Bahl R, Bhandari N, Saksena M et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. *J Pediatr* 2002; 141: 677–682.
Zinc-fortified oral rehydration salts solution was moderately efficacious in reducing the severity of acute diarrhea without increasing vomiting or reducing oral rehydration salts solution intake.
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77. Baqui AH, Zaman K, Persson LA et al. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. *J Nutr* 2003; 133: 4150–4157.

Iron + zinc was associated with lower risk of severe diarrhea, 19% lower in all infants and 30% lower in less well-nourished infants with weight-for-age Z-score below -1. A micronutrient mix containing 20 mg iron, 20 mg zinc, 1 mg riboflavin along with other minerals and vitamins was associated with a 15% higher risk of diarrhea in all infants and 22% higher risk in less well-nourished infants.

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Although there was satisfactory recovery in malnourished children with persistent diarrhea receiving the Khitchri-yogurt diet, there was no evidence of acceleration of recovery from diarrhea with zinc supplementation. In contrast, the reduction in plasma copper levels in zinc-supplemented malnourished children suggests that caution should be exercised in supplementing severely malnourished children with zinc alone.
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79. Ashraf H, Rahman MM, Fuchs GJ, Mahalanabis D. Folic acid in the treatment of acute watery diarrhoea in children: a double-blind, randomized, controlled trial. *Acta Paediatr* 1998; 87: 1113–1115.
No significant differences were observed in the intake of oral rehydration solution or stool output between the folic acid and placebo groups.
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80. Dewey KG, Domellof M, Cohen RJ et al. Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. *J Nutr* 2002; 132: 3249–3255.
Routine iron supplementation of breast-fed infants may benefit those with low Hb but may present risks for those with normal Hb in terms of diarrhea.
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81. Mitra AK, Akramuzzaman SM, Fuchs GJ et al. Long-term oral supplementation with iron is not harmful for young children in a poor community of Bangladesh. *J Nutr* 1997; 127: 1451–1455.
The two treatment groups did not differ in the number of episodes, mean duration of each episode, or total days of illness due to diarrhea. However, a 49% greater number of episodes of dysentery was observed with iron supplementation in a subset of the study children who were less than 12 months old ($P = 0.03$). The results of this study suggest that long-term oral iron supplementation is not harmful for older children in a poor community. Further studies are needed to demonstrate the safety and efficacy of iron administration in young infants.
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This is a systematic review and a key publication that concludes that iron supplementation has no apparent harmful effect on the overall incidence of infectious illnesses in children, though it slightly increases the risk of developing diarrhea.
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*The study suggests that *S. boulardii* significantly reduces the duration of acute diarrhea and the duration of hospital stay. *S. boulardii* seems to be a promising agent for the amelioration of the course of acute diarrhea in children when used therapeutically.*
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84. Cremonini F, Di Caro S, Covino M et al. Effect of different probiotic preparations on anti-helicobacter pylori therapy-related side effects: a parallel group, triple blind, placebo-controlled study. *Am J Gastroenterol* 2002; 97: 2744–2749.
*Helicobacter pylori (*H. pylori*) positive, asymptomatic patients who received probiotic supplementation (*Lactobacillus GG* or *Saccharomyces boulardii* or combination of *Lactobacillus spp.* and bifidobacteria) showed significantly lower incidence of diarrhea and taste disturbance during the eradication week with respect to the placebo group but were not associated with better compliance with antibiotic therapy. The effect of probiotic supplementation on side effects during anti-*H. pylori regimens* seemed to be independent of the probiotic species used.*
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85. Gaon D, Garmendia C, Murrielo NO et al. Effect of *Lactobacillus* strains (*L. casei* and *L. acidophilus* strains cerela) on bacterial overgrowth-related chronic diarrhea. *Medicina (B Aires)* 2002; 62: 159–163.
*This study provides evidence that *L. casei* and *L. acidophilus* strains are effective for treatment of bacterial overgrowth-related chronic diarrhea compared with placebo, and suggest that probiotics must be used with continuity.*
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86. Guandalini S, Pensabene L, Zikri MA et al. *Lactobacillus GG* administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. *J Pediatr Gastroenterol Nutr* 2000; 30: 54–60.
*Children (1 month to 3 years) with acute-onset diarrhea received either oral rehydration solution plus a live preparation of *Lactobacillus GG* (at least 10^{10} CFU/250 ml) or the same preparation plus placebo. Administering oral rehydration solution containing *Lactobacillus GG* resulted in shorter duration of diarrhea, less chance of a protracted course, and faster discharge from the hospital.*
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87. Guarino A, Canani RB, Spagnuolo MI et al. Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. *J Pediatr Gastroenterol Nutr* 1997; 25: 516–519.
*Children with mild diarrhea who were observed as outpatients received either oral rehydration or oral rehydration followed by the administration of lyophilized *Lactobacillus casei*, strain GG. The duration of diarrhea was reduced from 6 to 3 days in children receiving *Lactobacillus GG*. Six days after the onset of diarrhea, stools in only 4 out of 31 children who received *Lactobacillus GG* were positive for rotavirus compared with positive findings in 25 out of 30 control subjects.*
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88. Jirapinyo P, Densupsoontorn N, Thamonsiri N, Wongarn R. Prevention of antibiotic-associated diarrhea in infants by probiotics. *J Med Assoc Thai* 2002; 85 Suppl 2: S739–S742.

Infants and children with severe bacterial infections treated with broad-spectrum antibiotics who received probiotics had fewer diarrheal episodes (37.5%) than the control group (80%).

89. Kim HJ, Camilleri M, McKinzie S et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; 17: 895–904.
A probiotic formulation (VSL#3) (450 billion lyophilized bacteria/day) for 10 weeks reduced abdominal bloating in patients with diarrhea-predominant irritable bowel syndrome compared with placebo. No significant differences in mean gastrointestinal transit measurements, bowel function scores or satisfactory global symptom relief were seen between the groups.
90. Nopchinda S, Varavithya W, Phuapradit P et al. Effect of bifidobacterium Bb12 with or without Streptococcus thermophilus supplemented formula on nutritional status. *J Med Assoc Thai* 2002; 85 Suppl 4: S1225–S1231.
Children (aged 6–36 months) who received an infant formula with probiotics (Bifidobacteria Bb12 or Bb12 and Streptococcus thermophilus) showed better growth during a 6 month period.
91. Oberhelman RA, Gilman RH, Sheen P et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. *J Pediatr* 1999; 134: 15–20.
Undernourished children (6 to 24 months) received either Lactobacillus GG (L-GG) or placebo in flavored gelatin once daily, 6 days a week for 15 months. Subjects in the L-GG group had significantly fewer episodes of diarrhea compared with the placebo group. The decreased incidence of diarrhea was greatest in the 18- to 29-month age group and was largely limited to nonbreastfed children. L-GG supplementation may be useful as a prophylactic measure to control diarrhea in undernourished children at increased risk, especially nonbreastfed children in the toddler age group.
92. Rosenfeldt V, Michaelsen KF, Jakobsen M et al. Effect of probiotic Lactobacillus strains in young children hospitalized with acute diarrhea. *Pediatr Infect Dis J* 2002; 21: 411–416.
The mixture of two probiotics, Lactobacillus rhamnosus 19070-2 and Lactobacillus reuteri DSM 12246 (10^{10} colony-forming units of each strain twice daily for 5 days) ameliorated acute diarrhea in hospitalized children and reduced the period of rotavirus excretion. Oral bacteriotherapy was associated with a reduced length of hospital stay. The beneficial effects were most prominent in children treated early in the diarrheal phase.
93. Rosenfeldt V, Michaelsen KF, Jakobsen M et al. Effect of probiotic Lactobacillus strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. *Pediatr Infect Dis J* 2002; 21: 417–419.
In children with mild gastroenteritis attending day-care centers, the combination of lyophilized Lactobacillus rhamnosus 19070-2 and Lactobacillus reuteri DSM 12246 (10^{10} colony-forming units of each strain twice daily for 5 days) was effective in reducing the duration of diarrhea compared with placebo.
94. Szajewska H, Kotowska M, Mrukowicz JZ et al. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. *J Pediatr* 2001; 138: 361–365.
Children aged 1 to 36 months who were hospitalized for reasons other than diarrhea received either a Lactobacillus GG (LGG) supplement (6×10^9 colony-forming units) or a comparable placebo twice daily orally for the duration of their hospital stay. Prophylactic use of LGG significantly reduced the risk of nosocomial diarrhea, a major problem in pediatric hospitals worldwide, in infants, particularly nosocomial rotavirus gastroenteritis.
95. Urbancsek H, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomized study to evaluate the efficacy and safety of Antibiohilus in patients with radiation-induced diarrhoea. *Eur J Gastroenterol Hepatol* 2001; 13: 391–96.
Patients suffering from mild to moderate diarrhea induced by radiation therapy were supplemented with Lactobacillus rhamnosus (Antibiohilus) or placebo. There was a highly favourable benefit/risk ratio in favour of Antibiohilus.
96. Vanderhoof JA, Whitney DB, Antonson DL et al. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr* 1999; 135: 564–568.
Lactobacillus casei ssp. rhamnosus (Lactobacillus GG) (LGG) (1×10^{10} – 2×10^{10} colony forming units per day), or comparable placebo was administered to children between 6 months and 10 years of age with antibiotic-associated diarrhea (oral antibiotics administered for common childhood infections). Lactobacillus GG reduced the incidence of diarrhea compared with placebo treatment.
97. Chouraqui JP, Van Egroo LD, Fichot MC. Acidified milk formula supplemented with bifidobacterium lactis: impact on infant diarrhea in residential care settings. *J Pediatr Gastroenterol Nutr* 2004; 38: 288–292.
These results provide some evidence that viable Bifidobacterium lactis strain Bb 12, added to an acidified infant formula, has some protective effect against acute diarrhea in healthy children.
98. Correa NB, Peret Filho LA, Penna FJ et al. A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. *J Clin Gastroenterol* 2005; 39: 385–389.
There was a significant difference in the incidence of antibiotic-associated diarrhea in the children receiving probiotic-supplemented formula (16%) than nonsupplemented formula (31%). The authors conclude that prevention against antibiotic-associated diarrhea in infants was obtained by oral treatment with a daily dose of B. lactis and S. thermophilus.
99. Gaon D, Garcia H, Winter L et al. Effect of Lactobacillus strains and Saccharomyces boulardii on persistent diarrhea in children. *Medicina (B Aires)* 2003; 63: 293–298.

L. casei and *L. acidophilus* strains CERELA and *S. boulardii* are useful in the management of persistent diarrhea in children and the effect is not influenced by rotavirus status.

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100. Heiser CR, Ernst JA, Barrett JT, French N et al. Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhea. *J Int Assoc Physicians AIDS Care (Chic.Ill.)* 2004; 3: 121–129. *Probiotics, soluble fiber, and L-glutamine significantly reduced diarrhea for subjects receiving nelfinavir or lopinavir/ritonavir containing regimens. Nutritional co-therapies show a small clinical benefit in HIV-positive men with diarrhea.*
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101. Kotowska M, Albrecht P, Szajewska H. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2005; 21: 583–590. *S. boulardii reduced the risk of antibiotic-associated diarrhea compared with placebo in 269 children (aged 6 months to 14 years).*
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102. Plummer S, Weaver MA, Harris JC et al. Clostridium difficile pilot study: effects of probiotic supplementation on the incidence of *C. difficile* diarrhoea. *Int Microbiol* 2004; 7: 59–62. *On the basis of development of diarrhea, the incidence of samples positive for C. difficile-associated toxins was 2.9% in the probiotic group compared with 7.25% in the placebo group. When samples from all patients were tested (rather than just those developing diarrhea) 46% of probiotic patients were toxin-positive compared with 78% of the placebo group.*
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103. Rio ME, Zago LB, Garcia H, Winter L. [Influence of nutritional status on the effectiveness of a dietary supplement of live lactobacillus to prevent and cure diarrhoea in children]. *Arch Latinoam Nutr* 2004; 54: 287–292. *Although the fermented milk (L. acidophilus and L. casei) prevented half of the episodes in the controls but not in the undernourished, it was able to shorten the duration of diarrhea episodes and prevent protracted diarrhea irrespective of nutritional status.*
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104. Thibault H, Aubert-Jacquín C, Goulet O. Effects of long-term consumption of a fermented infant formula (with *Bifidobacterium breve* c50 and *Streptococcus thermophilus* 065) on acute diarrhea in healthy infants. *J Pediatr Gastroenterol Nutr* 2004; 39: 147–152. *Incidence, duration of diarrhea episodes and number of hospital admissions did not differ significantly between groups. Episodes were less severe in the fermented formula group. There were fewer cases of dehydration (2.5% versus 6.1%, $P = 0.01$), fewer medical consultations (46% versus 56.6%, $P = 0.003$), fewer ORS prescriptions (41.9% versus 51.9%, $P = 0.003$) and fewer switches to other formulas (59.5% versus 74.9%, $P = 0.0001$) in fermented formula infants compared with standard infant formula.*
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105. Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics* 2005; 115: 5–9. *The controls also had more diarrhea episodes and episodes of longer duration. The L reuteri group, compared with Bifidobacterium lactis or controls, had a significant decrease in number of days with fever, clinic visits, child care absences, and antibiotic prescriptions.*
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106. Xiao SD, Zhang dZ, Lu H et al. Multicenter, randomized, controlled trial of heat-killed *Lactobacillus acidophilus* LB in patients with chronic diarrhea. *Adv Ther* 2003; 20: 253–260. *At the end of the treatment, the clinical symptoms were markedly improved in the Lacteol group, indicating that L. acidophilus LB is more effective than living lactobacilli (Lacidophilin) in the treatment of chronic diarrhea.*
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107. Pereg D, Kimhi O, Tirosh A et al. The effect of fermented yogurt on the prevention of diarrhea in a healthy adult population. *Am J Infect Control* 2005; 33: 122–125. *The study showed that the incidence of diarrhea among healthy young adults consuming yogurt containing Lactobacillus casei is not significantly influenced.*
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108. Costa-Ribeiro H, Ribeiro TC, Mattos AP et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. *J Pediatr Gastroenterol Nutr* 2003; 36: 112–115. *No significant reduction in diarrhea duration and stool output were seen in children (less than 2 years of age) with moderate dehydration who received Lactobacillus GG in combination with oral rehydration solution compared with placebo. Our data imply that colonization must occur before benefits of probiotics can be realized. Probiotics are, therefore, likely to be of limited benefit in treating diarrheal illnesses of short duration such as viral enteritis. The beneficial effects of probiotics may be limited to prophylactic usage in high-risk populations.*
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109. Hatakka K, Savilahti E, Ponka A et al. Effect of long term consumption of probiotic milk on infections in children attending day-care centres: double blind, randomised trial. *Brit Med J* 2001; 322: 1327. *Healthy children aged 1–6 years received milk with or without Lactobacillus GG. The number of days with gastrointestinal symptoms did not differ between the two groups.*
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110. Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of *Saccharomyces boulardii* in the prevention of antibiotic-related diarrhoea in elderly patients. *J Infect.* 1998; 36: 171–174. *Patients over the age of 65 admitted to medical wards, and who were being prescribed antibiotics, received either Saccharomyces boulardii, a non-pathogenic yeast (113 g twice daily) or placebo for as long as they received antibiotics. There was no evidence that the concomitant use of Saccharomyces boulardii with antibiotics alters patients' bowel habits or prevents the appearance of Clostridium difficile toxin in the stool.*
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111. O'Sullivan MA, O'Morain CA. Bacterial supplementation in the irritable bowel syndrome. A randomised double-blind placebo-controlled crossover study. *Dig Liver Dis* 2000; 32: 294–301.

Supplementation with Lactobacillus casei strain GG did not significantly improve symptoms in irritable bowel syndrome patients compared with placebo.

112. Salazar-Lindo E, Miranda-Langschwager P, Campos-Sanchez M et al. Lactobacillus casei strain GG in the treatment of infants with acute watery diarrhea: a randomized, double-blind, placebo controlled clinical trial [ISRCTN67363048]. BMC Pediatr 2004; 4: 18.

This study did not show a positive effect of LGG on the clinical course of acute watery diarrhea in infants aged 3–36 months.

113. Salminen MK, Tynkkynen S, Rautelin H et al. The efficacy and safety of probiotic Lactobacillus rhamnosus GG on prolonged, noninfectious diarrhea in HIV patients on antiretroviral therapy: a randomized, placebo-controlled, crossover study. HIV Clin Trials 2004; 5: 183–191.

No significant differences in noninfectious diarrhea or gastrointestinal symptoms compared to placebo could be observed in this crossover study in HIV-infected patients with diarrhea for more than 1 month. Lactobacillus rhamnosus GG was used as probiotic but the sample size was very small.

114. Sudarmo SM, Ranuh RG, Rochim A, Soeparto P. Management of infant diarrhea with high-lactose probiotic-containing formula. Southeast Asian J Trop Med Public Health 2003; 34: 845–848.

There was no significant difference between the test (high-lactose Bifidobacterium bifidum) and control groups ($p > 0.05$) as well as at positive clinical test (13%) and positive floating test (65%). However, the patients receiving probiotic-containing formula had significantly less frequency of stools, when compared with the control group ($p < 0.05$).

115. Cuevas LE, Almeida LM, Mazunder P et al. Effect of zinc on the tuberculin response of children exposed to adults with smear-positive tuberculosis. Ann Trop Paediatr 2002; 22: 313–319.

PPD indurations were larger in children receiving zinc (mean 18.5 and 15.5 mm in the zinc and placebo groups, respectively) ($p < 0.03$). Mean induration sizes were larger in zinc-supplemented children, regardless of their nutritional status. The study demonstrates that zinc increases the PPD induration size in children irrespective of nutritional status.

116. Devi U, Mohan RC, Srivastava VK et al. Effect of iron supplementation on mild to moderate anaemia in pulmonary tuberculosis. Brit J Nutr 2003; 90: 541–550.

Iron supplementation may improve indices of iron status but ultimately recovery only takes place once tuberculosis is cured.

117. Chandra RK. Nutrient supplementation as adjunct therapy in pulmonary tuberculosis. Int J Vitam Nutr Res 2004; 74: 144–146.

At two months into the treatment, the group that was supplemented with a multivitamin/trace element preparation showed a significant reduction in the number of individuals with sputum smear positive for acid-fast bacillus: two out

of 22 individuals, compared with seven out of 22 among placebo-treated controls.

118. Hanekom WA, Hussey GD, Hughes EJ et al. Plasma-soluble CD30 in childhood tuberculosis: effects of disease severity, nutritional status, and vitamin A therapy. Clin Diagn Lab Immunol 1999; 6: 204–208.

Vitamin A-supplemented children demonstrated a mean (+/- standard error of the mean) decrease in sCD30 by a factor of 0.99 +/- 0.02 over 12 weeks, whereas a factor increase of 1.05 +/- 0.02 was demonstrated in the placebo group ($P = 0.02$). Nutritional compromise was associated with higher sCD30 levels and vitamin A therapy resulted in modulation of sCD30 levels over time.

119. Karyadi E, West CE, Schultink W et al. A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. Am J Clin Nutr 2002; 75: 720–727.

Vitamin A and zinc supplementation improves the effect of tuberculosis medication after 2 mo of antituberculosis treatment and results in earlier sputum smear conversion.

120. Mbala L, Matendo R, Nkailu R. Is vitamin B6 supplementation of isoniazid therapy useful in childhood tuberculosis. Trop Doct 1998; 28: 103–104.

The results of this study suggest that vitamin B6 supplementation of isoniazid therapy is unnecessary in childhood TB.

121. Morcos MM, Gabr AA, Samuel S et al. Vitamin D administration to tuberculous children and its value. Boll Chim Farm 1998; 137: 157–164.

The authors conclude that vitamin D therapy may be of great value in addition to antituberculous drugs in the treatment of tuberculous children.

122. Dugina NN, Chebotareva TV, Mitrokhin SD. [Large intestine dysbacteriosis and therapy efficacy in patients with respiratory tract tuberculosis in sanatoria]. Antibiot Khimioter 2004; 49: 35–38.

In this paper, published in Russian, it is recommended that the scheme of the treatment of patients with pulmonary tuberculosis in sanatoria should include corrigating agents and in particular probiotics containing live bifido- and lactobacteria having no contraindications and side effects, and providing elimination of intestinal dysbacteriosis.

123. Baeten JM, McClelland RS, Richardson BA et al. Vitamin A deficiency and the acute phase response among HIV-1-infected and -uninfected women in Kenya. J Acquir Immune Defic Syndr 2002; 31: 243–249.

HIV-1-infected women having an acute phase response had no increase in serum vitamin A levels after supplementation. Serum levels increased significantly among women without an acute phase response, although not to normal levels among women who were deficient at baseline.

124. Baeten JM, McClelland RS, Overbaugh J et al. Vitamin A supplementation and human immunodeficiency virus type

1 shedding in women: results of a randomized clinical trial. *J Infect Dis* 2002; 185: 1187–191.

No significant effect of supplementation on plasma HIV-1 load or CD4 or CD8 cell counts was observed, and no effect was seen among women who were vitamin A deficient at baseline. Vitamin A supplementation is unlikely to decrease the infectivity of women infected with HIV-1.

125. Baeten JM, McClelland RS, Corey L et al. Vitamin A supplementation and genital shedding of herpes simplex virus among HIV-1-infected women: a randomized clinical trial. *J Infect Dis* 2004; 189: 1466–1471.

Vitamin A supplementation is unlikely to decrease HSV shedding and infectivity.

126. Dreyfuss ML, Fawzi WW. Micronutrients and vertical transmission of HIV-1. *Am J Clin Nutr* 2002; 75: 959–970.

Randomized, placebo-controlled trials have reported that vitamin A and other vitamin supplements do not appear to have an effect on HIV transmission during pregnancy or the intrapartum period.

127. Duggan C, Fawzi W. Micronutrients and child health: studies in international nutrition and HIV infection. *Nutr Rev* 2001; 59: 358–369.

Vitamin A supplementation among communities at risk of deficiency effectively reduces mortality and morbidity in HIV-infected children. Vertical transmission of HIV has not to date been affected by maternal micronutrient supplementation.

128. Fawzi WW, Msamanga G, Hunter D et al. Randomized trial of vitamin supplements in relation to vertical transmission of HIV-1 in Tanzania. *J Acquir Immune Defic Syndr* 2000; 23: 246–254.

Vitamin A and multivitamins did not affect the risk of vertical transmission of HIV in utero nor during the intrapartum and early breastfeeding periods. Multivitamins resulted in a significant improvement in birth weight of babies who were HIV-negative at birth but had no effect among those who were HIV-positive.

129. Kennedy-Oji C, Coutoudis A, Kuhn L et al. Effects of vitamin A supplementation during pregnancy and early lactation on body weight of South African HIV-infected women. *J Health Popul Nutr* 2001; 19: 167–176.

Supplementation with vitamin A was not associated with improvements in prepartum weight gain but was significantly associated with improved weight retention three to six months after delivery.

130. Fawzi W, Msamanga G, Antelman G et al. Effect of prenatal vitamin supplementation on lower-genital levels of HIV type 1 and interleukin type 1 beta at 36 weeks of gestation. *Clin Infect Dis* 2004; 38: 716–722.

Multivitamin B-complex, C, and E had no effect on the risk of viral shedding. Significantly more women who received vitamin A had detectable levels of HIV-1 in CVL compared with those who did not receive vitamin A, these results raise concern about the use of vitamin A supplements by HIV-1-infected women.

131. Fawzi WW, Msamanga GI, Hunter D et al. Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child mortality. *AIDS* 2002; 16: 1935–1944.

Vitamin A increased the risk of HIV-1 transmission. Multivitamin (B, C, and E) supplementation of breastfeeding mothers reduced child mortality and HIV-1 transmission through breastfeeding among immunologically and nutritionally compromised women.

132. Allard JP, Aghdassi E, Chau J et al. Effects of vitamin E and C supplementation on oxidative stress and viral load in HIV-infected subjects. *AIDS* 1998; 12: 1653–1659.

Supplements of vitamin E and C reduce oxidative stress in HIV and produce a trend towards a reduction in viral load.

133. Fawzi WW, Villamor E, Msamanga GI et al. Trial of zinc supplements in relation to pregnancy outcomes, hematologic indicators, and T-cell counts among HIV-1-infected women in Tanzania. *Am J Clin Nutr* 2005; 81: 161–167.

Because of the lack of beneficial effects of zinc on adverse pregnancy outcomes and the likelihood of negative effects on hemoglobin concentrations, no compelling evidence exists to support the addition of zinc to prenatal supplements intended for pregnant HIV-infected women.

134. Kupka R, Msamanga GI, Spiegelman D et al. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. *J Nutr* 2004; 134: 2556–2560.

Plasma selenium levels were not associated with time to progression to CD4 cell count < 200 cells/mm³ but were weakly and positively related to CD4 cell count in the first years of follow up. Selenium status may be important for clinical outcomes related to HIV disease in sub-Saharan Africa.

135. Look MP, Rockstroh JK, Rao GS et al. Sodium selenite and N-acetylcysteine in antiretroviral-naive HIV-1-infected patients: a randomized, controlled pilot study. *Eur J Clin Invest* 1998; 28: 389–397.

Serum selenium levels increased significantly upon treatment. Viral load was not altered upon treatment.

136. Shor-Posner G, Lecusay R, Miguez MJ et al. Psychological burden in the era of HAART: impact of selenium therapy. *Int J Psychiatry Med* 2003; 33: 55–69.

Selenium therapy may be a beneficial treatment to decrease anxiety in HIV+ drug users who exhibit a high prevalence of psychological burden.

137. Olsen A, Mwaniki D, Krarup H, Friis H. Low-dose iron supplementation does not increase HIV-1 load. *J Acquir Immune Defic Syndr* 2004; 36: 637–638.

There was no effect on viral load, but effects of higher doses of iron cannot be excluded.

138. Baylin A, Villamor E, Rifai N et al. Effect of vitamin supplementation to HIV-infected pregnant women on the micronutrient status of their infants. *Eur J Clin Nutr* 2005; 59: 960–968.

Vitamin supplementation to HIV-1-infected women is effective in improving the vitamin status of infants during the first 6 months of age.

139. Fawzi W, Msamanga G, Spiegelman D et al. Transmission of HIV-1 through breastfeeding among women in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr* 2002; 31: 331–338.

Interventions that enhance immune reconstitution, such as micronutrient supplements, may be beneficial against transmission.

140. Fawzi WW, Msamanga GI, Spiegelman D et al. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998; 351:1477–1482.

Multivitamin supplementation is a low-cost way of substantially decreasing adverse pregnancy outcomes and increasing T-cell counts in HIV-1-infected women.

141. Fawzi WW, Msamanga GI, Spiegelman D et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med* 2004; 351: 23–32.

Multivitamin supplements (vitamins B,C,E) delay the progression of HIV disease and provide an effective, low-cost means of delaying the initiation of antiretroviral therapy in HIV-infected women.

142. Merchant AT, Msamanga G, Villamor E et al. Multivitamin supplementation of HIV-positive women during pregnancy reduces hypertension. *J Nutr* 2005; 135: 1776–1781.

Taking multivitamins containing vitamins B, C, and E during pregnancy may be an inexpensive and effective strategy to improve the health of the mother and baby.

143. Villamor E, Msamanga G, Spiegelman D et al. Effect of multivitamin and vitamin A supplements on weight gain during pregnancy among HIV-1-infected women. *Am J Clin Nutr* 2002; 76: 1082–1090.

Multivitamin supplementation during pregnancy improves the pattern of weight gain among HIV-infected women

144. Villamor E, Saathoff E, Bosch RJ et al. Vitamin supplementation of HIV-infected women improves postnatal child growth. *Am J Clin Nutr* 2005; 81: 880–888.

Supplementation of HIV-infected women with multivitamins (vitamin B complex, vitamin C, and vitamin E) during pregnancy and lactation is an effective intervention for improving ponderal growth in children.

145. Coutsoydis A, Pillay K, Spooner E et al. Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group. *AIDS* 1999; 13: 1517–1524.

Vitamin A supplementation, a low-cost intervention, does not appear to be effective in reducing overall mother-to-child transmission of HIV.

146. Friis H, Gomo E, Nyazema N et al. Effect of multimicronutrient supplementation on gestational length and birth

size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe. *Am J Clin Nutr* 2004; 80: 178–184.

The effect of multimicronutrient supplementation on birth weight was not significantly different between HIV-uninfected and HIV-infected, although multimicronutrient supplementation was associated with tendencies for increased gestational length, birth weight, and head circumference across the board.

147. McClelland RS, Baeten JM, Overbaugh J et al. Micronutrient supplementation increases genital tract shedding of HIV-1 in women: results of a randomized trial. *J Acquir Immune Defic Syndr* 2004; 37: 1657–1663.

Micronutrient supplementation resulted in higher CD4 (+23 cells/ μ L, $P = 0.03$) and CD8 (+74 cells/ μ L, $P = 0.005$) counts compared with placebo but did not alter the plasma viral load. In this randomized trial, micronutrients resulted in higher levels of genital HIV-1 shedding compared with placebo. Micronutrient supplementation resulted in higher CD4 and CD8 counts compared with placebo but did not alter the plasma viral load. In this randomized trial, micronutrients resulted in higher levels of genital HIV-1 shedding compared with placebo.

148. Jiamton S, Pepin J, Suttent R et al. A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. *AIDS* 2003; 17: 2461–2469.

Multiple micronutrient supplementation may enhance the survival of HIV-infected individuals with CD4 cell counts $<200 \times 10^6/l$.