

Effect of preventive supplementation with zinc and other micronutrients on malaria and diarrhoeal morbidity in African children

Jacobien Veenemans^{1*}

¹Wageningen University, Cell Biology and Immunology Group, The Netherlands

*jacobien.veenemans@gmail.com

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Thesis summary

Background

Zinc is important for innate and adaptive immune responses to infection. Preventive zinc supplementation has been shown to reduce the incidence of acute diarrhoea by 20%. Few trials have evaluated its effect against malaria. Because trial results for both outcomes are inconsistent, research priorities must shift from studies to measure efficacy to identifying factors that determine the magnitude of the effect of zinc supplementation. We hypothesized that protection by zinc supplementation depends on concomitant supplementation with other nutrients.

Objectives

Specific objectives were: a) to assess the effect of supplementation with zinc, alone or in combination with other nutrients, on the rates of malaria (primary objective); b) to assess intervention effects on rates of diarrhoea and other common diseases; c) to identify factors that determine the magnitude of the effect of the interventions. Our studies also provided an opportunity to assess effects of α^+ -thalassaemia on malaria and malaria-associated anaemia. This haemoglobin disorder is highly prevalent in eastern Africa and that has recently been reported to protect against severe malaria.

Methods

In a highly malaria-endemic area in rural Tanzania, we randomised children (n=612) aged 6-60 months with height-for-age z-score ≤ -1.5 SD to daily supplementation with:

a) zinc, vitamins and other mineral elements ('multi-nutrients'); b) zinc; c) multi-nutrients without zinc; or d) placebo. Those with *Plasmodium* infection at baseline were treated. Field staff and participants were blinded to treatment. Sick children were detected and evaluated in a research clinic. The primary outcome, an episode of malaria, was pre-defined as current *Plasmodium* antigenaemia in children with guardian-reported fever and any of the following: a) confirmed fever (axillary temperature ≥ 37.5 °C), or b) unconfirmed fever with inflammation (whole blood C-reactive protein concentrations ≥ 8 mg/L), separated by at least 14 days from a previous malaria episode.

Results

The primary analysis included 1,572 episodes of malaria and 526 child-years of observation. The prevalence of zinc deficiency (plasma zinc concentration < 9.9 $\mu\text{mol/mL}$) was 67% overall, and 60% in those without inflammation (plasma C-reactive protein concentration < 8 mg/L). This prevalence was dramatically reduced by zinc supplementation.

We found no evidence that concurrent supplementation with multi-nutrients influenced the magnitude of the effect of zinc on rates of malaria or diarrhoea, so that marginal effects will be presented in the remainder of this summary.

Although we found no evidence that zinc alone protected against malaria, it reduced rates of diarrhoea by 24% (95% CI: 4%-40%) and of episodes of fever without localising signs by 25% (4%-43%), two disorders with mutually exclusive case definitions.

We found no effect of multi-nutrients on the overall rate of malaria episodes, regardless the case definition used, but

the effect estimate was likely underestimated by children becoming asymptotically infected in the course of the intervention period. In the first 100 days of intervention, and in the analysis of first events, supplementation with multi-nutrients, with or without zinc, increased the hazard of malaria by one-third. In addition, subgroup analysis indicated that this effect depended strongly on age and iron status at baseline, with rates of episodes with parasite densities $> 10,000$ parasites/ μL increasing by 27% (1%-61%) and 53% (11%-111%) in the youngest children (6-17 months) and in children with iron deficiency, whilst there was no evident effect in older children or those without iron deficiency (p-values for interaction: 0.02 and 0.007).

Despite the increase in malaria rates, the children who had the lowest haemoglobin concentrations during malaria (those aged 6-17 months) were better able to maintain their haemoglobin concentrations when having received multi-nutrients. Direct epidemiological evidence is lacking, however, if and under what conditions the higher haemoglobin concentrations during malaria (and expected reduced risk of death due to severe malarial anaemia) outweigh the possible increase in other potentially lethal disease manifestations.

Multi-nutrient supplementation seemed to increase the rate of diarrhoea by 19% (-6% to 50%). Subgroup analysis indicated that this effect depended on *Giardia intestinalis* infection at baseline (p-values for interaction: 0.03): in those without multi-nutrients, infection was associated with a reduction in rates of diarrhoea by 68% (34%-85%), whilst there was no evidence for such protection in those receiving multi-nutrients. Similar effect modification was found for fever without localizing signs.

Of 612 children in the trial, 50% had normal genotype, whilst 41% and 9% were heterozygote and homozygous, respectively, for α^+ -thalassaemia. We found no evidence of group differences in malaria rates between genotypes. Subgroup analysis suggested, however, that the effect of α^+ -thalassaemia depended on age. Thus in children below 18 months, malaria rates were increased by 30% (2%-65%) in heterozygotes, whereas they were decreased by 20% (5%-32%) in older children (p-value for interaction: 0.001). Similar patterns were found for homozygotes, even though estimates were less precise due the smaller numbers of children in this age class. Based on data from a pilot survey and a study in Kenya, we found that children with α^+ -thalassaemia (particularly homozygotes) were protected against the decline in haemoglobin concentration associated with mild to asymptomatic infections, particularly when these infections were accompanied by inflammation.

Interpretation and conclusions for policies

We found no evidence that addition of vitamins and other mineral elements increased the health benefits of zinc sup-

plements. The beneficial effects of zinc described in this thesis strengthen the case for scaling up zinc interventions in deficient populations of African children, without concerns that it will cause adverse effects due to malaria.

Multi-nutrient supplementation may be unsafe in malaria-endemic areas, particularly in young children with iron deficiency. Thus the recommendation by the World Health Organization that iron supplements should be administered routinely to iron-deficient infants in settings with adequate access to anti-malarial treatment is insufficiently supported by evidence and should be reconsidered. Our results underscore that supplementation or home fortification, even when targeting deficient subgroups in settings with access to adequate primary care, should not be recommended in malaria-endemic areas until their safety has been demonstrated.

Publications resulting from this thesis (as per 31 August 2012):

- Veenemans J, Schouten LRA, Ottenhof MJ, Mank TG, Uges DRA, Mbugi EV, Demir AY, Kraaijenhagen RJ, Savelkoul HFJ, Verhoef H. Effect of preventive supplementation with zinc and other micronutrients on non-malarial morbidity in rural Tanzanian pre-school children: a randomized trial. *PLoS ONE* 2012, **7**: e41630.
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