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

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Summary

Background **Studies from Asia have suggested that zinc supplementation can reduce morbidity and mortality in children, but evidence from malarious populations in Africa has been inconsistent. Our aim was to assess the effects of zinc supplementation on overall mortality in children in Pemba, Zanzibar.**

Methods **We enrolled 42 546 children aged 1–36 months, contributing a total of 56 507 child-years in a randomised, double-blind, placebo-controlled trial in Pemba, Zanzibar. Randomisation was by household. 21 274 children received daily supplementation with zinc 10 mg (5 mg in children younger than 12 months) for mean 484·7 days (SD 306·6). 21 272 received placebo. The primary endpoint was overall mortality, and analysis was by intention to treat. This study is registered as an International Standard Randomised Clinical Trial, number ISRCTN59549825.**

Findings **Overall, there was a non-significant 7% (95% CI –6% to 19%; p=0·29) reduction in the relative risk of all-cause mortality associated with zinc supplementation.**

Interpretation **We believe that a meta-analysis of all studies of mortality and morbidity, will help to make evidence-based recommendations for the role of zinc supplementation in public health policy to improve mortality, morbidity, growth, and development in young children.**

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Introduction

Pneumonia, diarrhoea, and malaria account for 45% of the 10·6 million yearly deaths of children younger than 5 years despite some success with preventive and therapeutic interventions.[1] 2·6 million of these deaths take place in Africa,[1] including 90% of the 0·8 million worldwide childhood malaria deaths every year.[2] Identification of low-cost interventions that would reduce such mortality, and help countries achieve the Millennium Development Goal of two-thirds reduction in child mortality,[3] is a priority.

Deficiency of a few essential micronutrients is recognised to greatly increase the risk of morbidity and mortality from infectious diseases in developing countries. Evidence for zinc as one such important micronutrient has emerged; in addition to data linking zinc deficiency to growth retardation and impairment of immune function,[4] zinc supplementation has shown significant reduction in rates and severity of diarrhoea[5] and pneumonia[5,6] (the two main causes of under-5 mortality). Reports from three small trials in Asian populations without malaria noted that zinc supplementation significantly reduced child mortality.[7–9] Evidence for the benefit of zinc supplementation on malaria morbidity has been inconsistent.[10–12] We therefore undertook a community-based trial to assess the effect of zinc supplementation on mortality in children aged 1–48 months in Pemba, Zanzibar, a place with a high-frequency of malaria transmission.

Methods

Participants

The study was undertaken in Pemba, the smaller of the two islands of the Zanzibar archipelago, with a population of about 350 000, most of whom are African, and Shirazi Muslims. A baseline census of this island suggested an infant mortality rate of 89 per 1000 livebirths. Malaria is holoendemic and has year-round transmission that is highest from June to September, after the Spring rainy season (March–May). The frequency of malaria transmission is representative of coastal east Africa, where a yearly inoculation rate of 405 infective bites per person has been described.[13] *Plasmodium falciparum* accounts for nearly all serious clinical malaria.

From January to December, 2001, we mapped and censused the whole island, and assigned unique numbers to all houses; the island was divided into working areas (clusters) and one female community worker was responsible for one cluster. Details of the study design have been previously reported.[14] Parents of eligible children, those aged 1–35 months, who were likely to remain resident on the island and did not have severe malnutrition needing rehabilitation (defined as Kwashiorkor, noted by the enrolment worker), were invited to participate in the study. Enrolment was undertaken one district at a time, starting on Jan 1, 2002 and finishing the initial enrolment on June 29, 2002. All children aged 1–35 months were enrolled if parents gave consent. A study worker read the consent statement to the primary

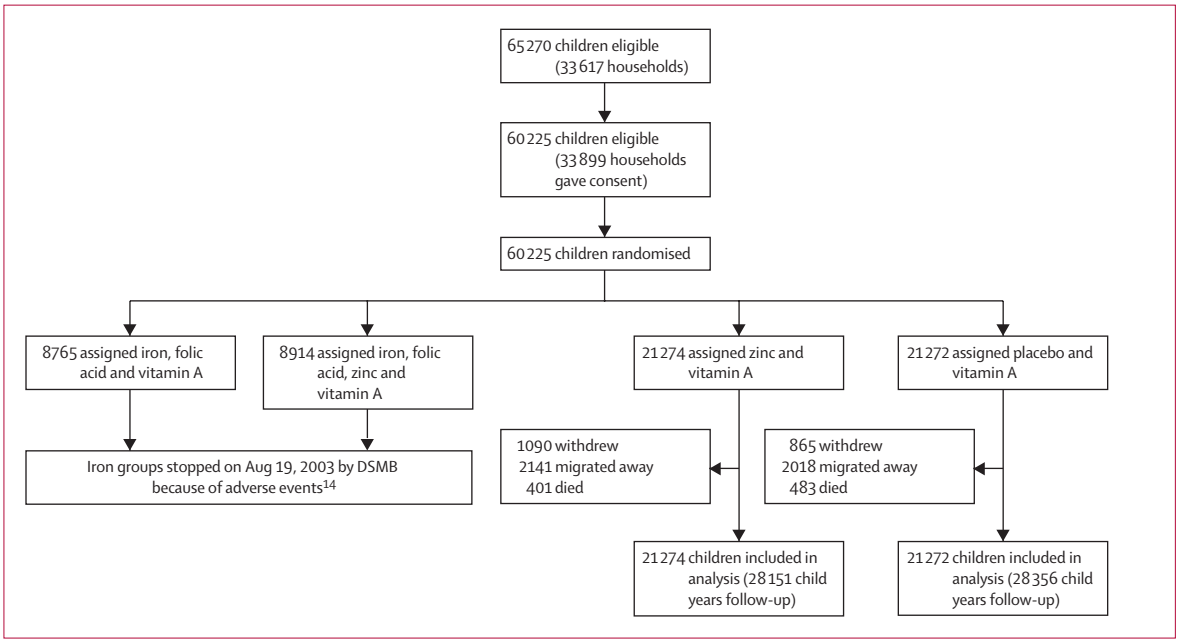

Figure 1: **Trial profile**

caregiver and then signed the consent form if consent was given. The study was approved by the Johns Hopkins committee on human research, the WHO ethical review committee, and the Zanzibar Research Council.

Procedures

The study was a double-blind randomised trial with four arms: iron, folic acid, and zinc (IFAZ); iron and folic acid (IFA); zinc; and placebo. The primary endpoint was all-cause deaths. On recommendation of the Data and Safety Monitoring Board (DSMB), the IFAZ and IFA groups were stopped on Aug 19, 2003 because of overwhelming evidence of increased hospital admissions and a trend for increased mortality associated with iron supplementation; the results from these groups were subsequently reported.[14]

Children from the IFAZ and non-zinc IFA groups were switched to the zinc and placebo groups, respectively. The halting of the IFAZ and IFA arms and switching of children to the other groups were done with the help of WHO and the DSMB statistician. The trial initially used 16-letter codes (four-letter codes assigned to the individual supplementation groups) and two-stage blinding. The four-letter codes for every group were known only to WHO and the manufacturer; the pharmacy dispensing the supplements knew only which letter code was assigned to each child, and the study worker and family knew neither. At the time of switch, WHO and the DSMB statistician provided an alternative letter code for all of the redundant eight-letter codes. The zinc and placebo groups continued, on recommendation of the DSMB, until Sept 30, 2005 and we report results for the primary and secondary (cause-specific) mortality outcomes of these groups.

The supplement was a dispersible (dissolves in water or breast-milk in about 20 s) tablet containing 10 mg of elemental zinc sulphate, manufactured by Nutriset, Bierne, France in scientific collaboration with WHO. The zinc-containing tablets and the placebo tablets were provided in blister strips. Tablets of both groups were similar in packaging, appearance, taste, and inactive ingredients. Children aged 12 months or older were given one tablet a day; children aged younger than 12 months were given a half tablet a day. The tablet was dissolved in 5–10 mL of water or breast milk. All children aged 12 months or older were given 200 000 IU of vitamin A every 6 months; children aged 6–11 months were given 100 000 IU. Children received zinc or placebo supplements until they were 48 months of age.

Randomisation was by household, by an allocation sequence (permuted block randomisation with block length of 16) computer-generated by WHO. The blister strips were coded with one of the letter codes, and every child was assigned a letter on enrolment on the basis of randomisation sequence. Labels with the child's identification were attached by the pharmacy to the supplement strips.

A card with the child's and household's identification information and a control number for verification was provided to each child. The family was asked to maintain this card, show it to the community worker during visits, and present it if the child was taken to hospital. Three grades of supervisor, all of whom were mobile on motorbikes, ensured flow of information and supplies to and from the participants. The children were visited every week at home by a community worker who delivered a strip of seven tablets labelled with the child's

identification, obtained the previous week's strip, and recorded the mother's report of tablets consumed in the past week. These reports, and the presence of any tablets remaining in the blister pack, were used to record adherence. On such home visits, workers also obtained information about hospital admissions and deaths of study children. Reports of hospital admissions were given to study staff to compare with information from hospital surveillance. Reports of deaths were given to two supervisors who were trained to do post-mortem interviews with the family to establish the cause of death; a standard instrument[15] was adapted for local use, pretested, and administered within 2 months of the child's death.

All five hospitals on the island were monitored by teams of two hospital staff and two full-time supervisors employed by the project to be present in the paediatric ward for 18 hours a day. For all admissions to the paediatric ward, standard study procedures included confirmation of the identity of the child, tracking the child throughout their hospital stay, and recording cause of death, if necessary.

The primary outcome was overall mortality in participating children aged 1–48 months. Deaths were counted if they took place during the supplementation period or within 30 days of stopping supplementation, irrespective of adherence to supplement. Secondary outcomes were age-specific, sex-specific, and cause-specific mortality. On the basis of previous evidence, we analysed deaths in two age groups (children younger than 12 months and those 12 months or older), which were selected before starting the study and specified in the protocol. Cause of death was ascertained by post-mortem interview and hospital records. Three teams that consisted of two physicians and a medical assistant, independently assigned one primary and two secondary causes of death. Any disagreements were resolved by discussion. These teams did not include investigators and were masked to supplement allocation.

The sample size of the original trial (with iron supplementation) was designed to detect a reduction in overall mortality of 20% with 90% power, a 5% two-sided type I error, 10% loss to follow-up, a design effect of 1·05, and the assumption of no interaction of iron and zinc affecting mortality (baseline mortality rate 15·3/1000) in children aged 1–48 months. To meet these criteria, we needed a sample size of about 15 000 person-years in each group for the marginal comparisons of the zinc arms versus the non-zinc arms. At the second DSMB meeting, 14 months into recruitment, we noted that the mortality rate was substantially lower than originally expected. We then recalculated the sample size estimates, which were about 30 000 person-years in marginal comparisons for 20% reduction and 90% power. After the IFA-containing arms were stopped, marginal comparisons were not valid, so recruitment and follow-up for the effects of the zinc supplement were continued to accumulate the required

	Zinc group			Placebo group		
	Boys	Girls	All	Boys	Girls	All
Total enrolment (n)	10 681	10 593	21 274	10 743	10 529	21 272
Age at enrolment (months)						
0–11	6668	6626	13 294	6734	6584	13 318
≥12	4013	3967	7980	4009	3945	7954
Adherence	80%	80%	80%	82%	82%	82%
Education (illiteracy)						
Father	3812 (36%)	3793 (36%)	7605 (36%)	3770 (35%)	3761 (36%)	7531 (35%)
Mother	4556 (43%)	4469 (42%)	9025 (42%)	4534 (42%)	4454 (42%)	8988 (42%)
History of sleeping under bed net						
Always	2907 (27%)	2850 (27%)	5757 (27%)	2802 (26%)	2883 (27%)	5685 (27%)
Sometimes	1211 (11%)	1237 (12%)	2448 (12%)	1272 (12%)	1175 (11%)	2447 (12%)
Anthropometric status*						
Normal	216 (64%)	253 (72%)	469 (68%)	220 (63%)	264 (70%)	484 (66·8%)
Wasted	19 (6%)	23 (7%)	42 (6%)	20 (6%)	23 (6%)	43 (5·9)
Stunted	91 (27%)	74 (21·0%)	165 (24%)	101 (29%)	82 (22%)	183 (25·2%)
Wasted and stunted	11 (3%)	3 (1%)	14 (2%)	8 (2%)	7 (2%)	15 (2·1%)
Haemoglobin* (g/L)	96·5 (12·9)	98·7 (13·3)	97·6 (13·2)	96·6 (13·3)	98·8 (13·0)	97·7 (13·2)
Zinc protoporphyrin* (µmol/M of haem)	146·0 (103·4)	131·96 (79·4)	138·8 (92·2)	149·27 (97·6)	138·31 (91·5%)	143·48 (94·5)
Plasma zinc concentration* (µmol/L)	11·99 (5·1)	11·88 (4·2)	11·93 (4·6)	11·99 (4·6)	12·17 (4·8)	12·09 (4·73)
Serum ferritin concentration* (µg/L)	55·39 (77·6)	52·4 (62·8)	53·9 (70·5)	50·3 (54·2)	56·6 (66·0)	53·6 (60·7)

Data are n (%) or mean SD. Percentages do not necessarily add up to 100% because of rounding. *Restricted to a subgroup of substudy children (n=1066). A person was designated as literate if they had had some schooling and could read and write.

Table 1: **Baseline characteristics of children assigned zinc and placebo**

	Zinc group		Placebo group		Relative risk	95% CI	p
	Deaths	Rate per 100 child-years	Deaths	Rate per 100 child-years			
Overall	401	1·42	433	1·53	0·93	(0·81–1·06)	0·294
Age (months)							
0–11	204	3·55	192	3·36	1·06	(0·87–1·29)	0·566
≥12	197	0·88	241	1·06	0·82	(0·68–1·00)	0·045
Sex							
Boys	175	1·23	218	1·52	0·81	(0·66–0·99)	0·04
Girls	226	1·62	215	1·54	1·05	(0·87–1·26)	0·605
Sex and age (months)							
Boys							
0–11	86	3·00	91	3·15	0·95	(0·71–1·28)	0·751
≥12	89	0·78	127	1·11	0·71	(0·54–0·93)	0·013
Girls							
0–11	118	4·11	101	3·58	1·15	(0·88–1·50)	0·296
≥12	108	0·98	114	1·02	0·95	(0·73–1·24)	0·722

Table 2: **Effect of zinc supplementation on overall mortality and by sex and age groups**

sample size of 45 000 child years of follow-up for the original zinc and placebo arms.

A substudy of 4000 children, assessed in more detail than the others, consisted of a random sample of clusters in all four districts selected after the census. Detailed methods have been reported previously.[14] Supplementation and adverse event surveillance was the same as in the main trial. Children in the substudy visited a study clinic for baseline assessment, including physical examination, height and weight measurements, and parental interview by a physician or clinician and trained health worker; a 3 mL venous blood sample was obtained from the child for comprehensive haematological analysis, erythrocyte zinc protoporphyrin measurement, and malaria parasite count.

Statistical analysis

A data entry system enabled all information gathered in the community to be entered by the end of the next day.[14] The system had many range and logic checks, and any errors were corrected by field or hospital staff on a daily basis. For all outcomes, double data entry was used. We did an intention-to-treat analysis. For children who migrated away from the trial location, withdrew, or died, data were included until they left the study. Person-time analysis was done with the time the child was followed-up as denominator. For the effect on total mortality and cause-specific mortality, we used Anderson Gill time-to-event survival methods in Cox regression[16] with robust estimation of SE to account for multiple events per household (SAS version 9.0, STATA version 8.2). In these analyses, a relative rate of less than 1 was consistent with protection in the zinc group compared with the placebo group. To assess the effect of duration of supplementation on intervention effects, Nelson-Aalen cumulative hazard estimates were calculated and graphically presented[17] with STATA version 8.2.

We assessed the interaction of the effect of Z with age and sex by Mantel-Cox comparison between subgroups, estimating χ^2 for unequal relative rates (effect modification) and its p value (STMC procedure in STATA version 8.2).

We did analyses of both primary cause of death (established by verbal post-mortem assessment) and any cause of death (more than one cause could have contributed to the death). Since the results of these two analyses were very similar, only those for the primary cause of death are presented.

This study is registered as an International Standard Randomised Clinical Trial, number ISRCTN59549825.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. WHO coordinated the preparation and delivery of supplements and organisation of DSMB meetings.

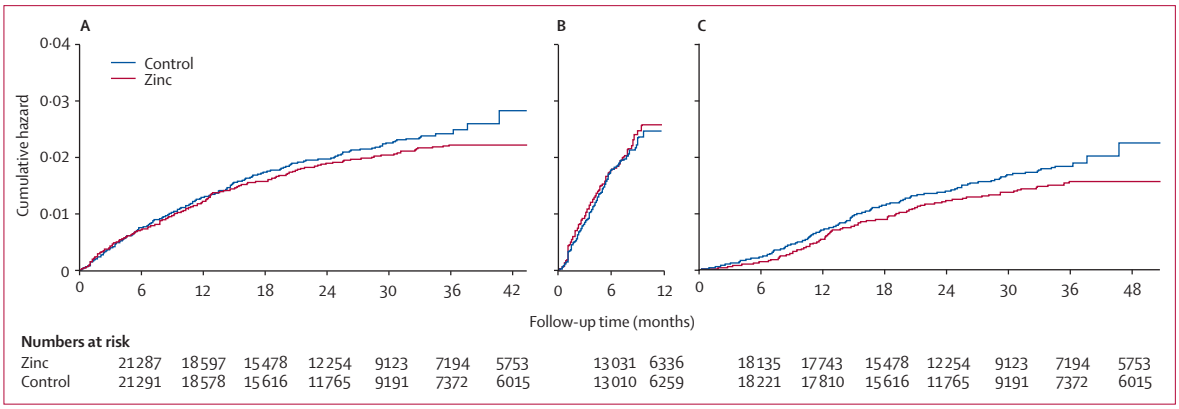

Figure 2: **Nelson-Aalen estimates and curves of mortality in zinc and placebo groups**
(A) all children; (B) children aged <12 months; and (C) children aged ≥12 months.

Results

Of 33 617 households contacted, 91·9% consented to participate, leading to a total enrolment of 60 225 children; 42 546 children were enrolled in the two arms included in this analysis (zinc and placebo), contributing a total follow-up of 56 507 child-years (figure 1). The mean duration of supplementation was 484·7 days (SD 306·6; 10 and 90 percentile=110 and 952 days, respectively). The two groups were similar for all measured baseline characteristics (table 1), including use of bednets, transfusions in previous 6 months (107 for zinc, and 128 for placebo) and reported hospital admissions in the previous 6 months. Adherence for consumption of supplements during follow-up (proportion of follow-up days supplement was consumed) was similar between the two arms. To account for age and sex interactions of treatment effects, we also assessed the baseline features by sex (table 1) and age (data not shown), which revealed comparability at baseline by age and sex subgroups.

The mortality rate in the placebo group was 15·3 per 1000 child-years at risk. Of 834 deaths in study children, 155 (19%) took place in hospital. Overall, there was a non-significant 7% (95% CI –6% to 19%) reduction in the relative risk of all-cause mortality associated with zinc supplementation (table 2). However, this risk seemed to differ marginally between children younger than 12 months (–6% [–29% to 13%]) and children aged 12–48 months (18% [0% to 32%]); p=0·071. The effect on mortality also marginally differed by sex, being –5% (95% CI –26% to 13%) for girls and 19% (1% to 34%) for boys; p=0·063. We calculated Nelson-Aalen cumulative hazard estimates for effect of duration of supplementation on intervention effects overall, for age younger than 12 months and 12–48 months (figure 2). In infants, data were similar in those aged less than 6 months and those aged 6–12 months (data not presented).

Overall, there were non-significant trends for lower mortality due to malaria, other infections, and, diarrhoea in the zinc group than in the placebo group (table 3). Cause-specific mortality analysis in the subgroups (table 3) suggested that, in the subgroups that had a significant change in total mortality, the effect was not restricted to a specific cause (figure 3), but contributed mainly by malaria, other infections, and to lesser extent diarrhoea. Of 84 deaths attributed to other infections, 47 were due to pneumonia and 18 to sepsis, meningitis, measles, or pertussis; 19 deaths were attributable to indeterminate febrile illness.

	Deaths*		RR (95% CI)	p
	Zinc group	Placebo group		
Malaria-related causes	272 (1·3%)	302 (1·4%)	0·90 (0·77–1·06)	0·236
Boys	116 (1·1%)	149 (1·4%)	0·79 (0·62–1·00)	0·053
Girls	156 (1·5%)	153 (1·5%)	1·02 (0·82–1·27)	0·865
Age 0–11 months	130 (1%)	138 (1%)	0·94 (0·74–1·19)	0·609
Age ≥12 months	142 (1·8%)	164 (2·1%)	0·87 (0·70–1·09)	0·24
Other infections†	35 (0·2%)	49 (0·2%)	0·72 (0·46–1·11)	0·133
Boys	15 (0·1%)	27 (0·3%)	0·56 (0·30–1·05)	0·073
Girls	20 (0·2%)	22 (0·2%)	0·91 (0·49–1·66)	0·748
Age 0–11 months	24 (0·2%)	26 (0·2%)	0·92 (0·53–1·60)	0·769
Age ≥12 months	11 (0·1%)	23 (0·3%)	0·48 (0·23–0·99)	0·046
Diarrhoea	16 (0·1%)	18 (0·1%)	0·89 (0·45–1·74)	0·739
Boys	10 (0·1%)	11 (0·1%)	0·92 (0·39–2·15)	0·846
Girls	6 (0·1%)	7 (0·1%)	0·85 (0·29–2·54)	0·775
Age 0–11 months	11 (0·1%)	8 (0·1%)	1·37 (0·55–3·41)	0·497
Age ≥12 months	5 (0·1%)	10 (0·1%)	0·50 (0·17–1·47)	0·21
Other causes	27 (0·1%)	20 (0· %)	1·36 (0·76–2·42)	0·30
Boys	12 (0·1%)	8 (0·1%)	1·51 (0·62–3·70)	0·362
Girls	15 (0·1%)	12 (0·1%)	1·25 (0·59–2·68)	0·560
Age 0–11 months	13 (0·1%)	6 (0·1%)	2·16 (0·82–5·69)	0·118
Age ≥12 months	14 (0·2%)	14 (0·2%)	1·01 (0·48–2·12)	0·982

RR=relative risk. *Data are number (%). †Includes pneumonia, meningitis, septicaemia, bacteraemia, pertussis, measles. For pneumonia zinc=22 deaths, placebo=25 deaths. RR 0·88 (95% CI 0·5–1·5, p=0·667).

Table 3: **Effect of zinc supplementation on cause-specific mortality**

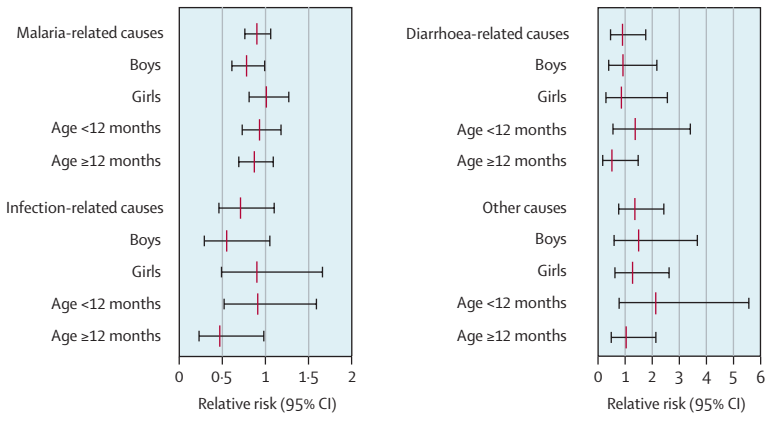

Figure 3: **Effect of zinc supplementation on cause-specific mortality overall and in subgroups**

Discussion

In our study, zinc supplementation did not result in a significant reduction in overall mortality in children aged 1–48 months in a population with high malaria transmission. However, there was a suggestion that the effect varied by age, with no effect on mortality in infants, and a marginally significant 18% reduction of mortality in children 12–48 months of age (p=0·045). This effect was mainly a consequence of fewer deaths from malaria and other infections. Any effect on mortality in this trial was in addition to a possible effect of vitamin A supplementation that both groups received according to recommendations. That the verbal autopsy had low specificity for identification of malaria-related deaths needs to be borne in mind. However, the common error is misclassification between malaria and other febrile infections. Since both types of illness were counted, misclassification would probably not affect overall conclusions. We powered our study on the basis of earlier preliminary results for a 20% reduction in mortality, and therefore, we did not have sufficient power

to detect a smaller, but still clinically important, say 10%, relative reduction in total mortality.

The effect of zinc supplementation on prevention of morbidity from diarrhoea[5,18] and pneumonia[5,6] in developing country setting has previously been shown.[5] Many trials of daily or weekly zinc supplementation in low income settings have been reported and nearly all noted a reduced frequency of diarrhoea and pneumonia when these outcomes were assessed. Three trials of zinc from Africa with diarrhoea or pneumonia outcomes, or both[12,19,20] showed significant effects on diarrhoea, and one that assessed pneumonia in children with protein energy malnutrition reported a beneficial effect.[20]

Trials on prevention of malaria morbidity have produced conflicting results. A trial in Papua New Guinea reported that zinc supplementation significantly reduced the frequency of clinic visits for malaria associated with *P falciparum* and noted greatest effectiveness of zinc in ill children with high-density parasitaemia.[11] An earlier study in the Gambia had also reported a non-significant reduction in malaria clinic visits in the zinc-supplemented group compared with the placebo group ($p=0\cdot07$).[10] In Uganda, zinc-supplemented children had non-significantly fewer infections (82% of which were malaria) than children given placebo.[21] In Burkina Faso, zinc supplementation had no effect on childhood malaria morbidity diagnosed at home visits.[12]

During the past 5 years, three studies of zinc supplementation, which were not powered by design to assess mortality, did find significant effects on mortality. A study in full term, small for gestational age children in India noted a 68% relative reduction in mortality compared with control[7] and two studies from Bangladesh, one with zinc as treatment for diarrhoea[8] and the other with weekly zinc supplementation[9] recorded 50% and 80% relative reductions in mortality, respectively. Two other small trials had results suggestive of mortality reduction. A study in Brazil in low birthweight children showed a 50% relative mortality reduction.[22] In the Burkina Faso trial, although there was no effect on malaria morbidity, a 59% lower relative mortality in the zinc group was seen.[12]

After iron, zinc is the second most abundant trace element in the body and it mediates many different physiological functions. It is a necessary component of many metallo-proteins, including those important for DNA replication and cell division, and is crucial for maintenance of immunological integrity. In studies of zinc deficiency, the production of tumour necrosis factor-α, interferon-C and interleukin-2 by peripheral blood mononuclear cells, which are all Th1 products, are decreased, whereas products of Th2 cells (interleukin-4, interleukin-6 and interleukin-10) are unaffected.[23] These changes, however, are easily reversed with zinc supplementation.[23]

Because of its role in maintenance of cell integrity and immunity, zinc is thought to play an important part in the prevention of infectious diseases. The effect of zinc on diarrhoea might also be related to its role in water and electrolyte transport, intestinal permeability,[24] enzyme functions of enterocytes,[25] enhanced intestinal tissue repair,[26] or enhanced local immunity restricting bacterial overgrowth and causing early pathogen clearance. More than one of these mechanisms could be implicated.

The interaction between zinc effects and age is consistent with findings of no significant effect on diarrhoea morbidity in children aged 6–11 months in the previous pooled analysis of trials.[5] Other studies assessing the effect of zinc in children aged 0–6 months have also recorded no effect both in prevention[27] and therapy of diarrhoea.[28,29] Our study consisted of a large number of children, so insufficient power to detect an effect in infants unlikely to explain our results. There are several possible explanations for the absence of effects of zinc supplementation in children younger than 12 months. Infants might have acquired adequate zinc in utero (there is preferential zinc shunting across the placenta[30]) and are able to obtain adequate zinc from breast milk, even when maternal stores are suboptimum.[31] Since breastfeeding rates were 95% or greater until the infant was aged 12 months in the study population, we cannot compare the effects of zinc supplements between breastfed and non-breastfed infants. Alternatively, the absence of effect in this age group might be related to the low 5 mg dose used, compared with 10–20 mg given in previous studies, in which effects on morbidity or mortality were seen.

During infancy, the cellular immune system matures, with a shift from Th2 predominant immunity at birth to predominantly Th1 immunity by age 2 years.[32] Effects of zinc might be mediated through improvement in immunity by stimulating optimum Th1/Th2 balance and this effect could be restricted in infants because of intrinsic limitations in the capacity of infants to produce interferon[33] and other Th1 (interleukin-2, interleukin-12) interleukins.[34] As the maturation of the immune system is at least partly driven by the exposure of children to microorganisms,[35] variation in response to zinc supplements in infants in different populations might be expected. Our findings of no effect in infants need further investigation with existing datasets, and in subsequent studies because they could have important implications for targeting of children who would benefit from additional zinc.

The apparent differences in the effect of zinc supplementation by sex, with a benefit in boys and no benefit in girls, could possibly be due to chance, but are consistent with previous studies recording substantial effects of zinc supplementation on growth,[36] diarrhoea morbidity[18] and respiratory morbidity[37] in boys. Nutritional and immunological differences might affect responses to infections and survival. Estimated zinc requirements for infant growth are higher for boys than for girls, which has been suggested as a possible reason for greater effect in boys.[38] However, plasma zinc concentrations have not shown a large differential between boys and girls.[5] Sex differences in effects on mortality have been recorded for vitamin A supplementation,[39] iodine supplementation[40]

and are also related to non-specific mortality effects of measles,[41] hepatitis B[42] and DTP vaccinations.[43] Little is known about possible mechanisms for the biological basis of these effects. Animal models of malaria,[44] respiratory syncytial virus[45] and influenza[46] suggest that Th1-mediated immunity is protective against severe disease, whereas Th2-mediated immunity increases susceptibility to disease. Such animal models also suggest that female mice might have a stronger Th2 profile than male mice.[47] Antibody-dependent cellular cytotoxicity antibody titres have been noted to be lower in young females during acute infection[48] and after vaccination.[49] These findings suggest that sex differences in effects of zinc supplementation could be mediated through differential effects on the immune system.

Thus, the results of this large community-based placebo-controlled zinc supplementation trial suggest that in settings with high-frequency malaria transmission typical of sub-Saharan Africa, zinc supplementation did not have any effect on mortality in infants, but there was a suggestion of reduced mortality in children older than 1 year. Feasible and sustainable methods of enhancing the bioavailable intake of dietary zinc need assessment. We also need to know whether a higher dose would have a different effect in infants, and to elucidate the mechanisms of the effects of zinc and any differences between boys and girls. Our results suggest a need for meta-analysis of all available studies both for mortality and morbidity to make evidence-based recommendation for public health policy to improve mortality, morbidity, growth, and development.

Contributors

S Sazawal and R E Black coordinated the trial, and made primary contributions to development, rationale, design, execution, analysis, and writing. R J Stoltzfus contributed to study design. A Dutta contributed to implementation of the trial, design of surveillance systems, quality control, and with U Dhingra was responsible for programming, data management, and analysis. M Ramsan, H M Chwaya, Mashavi K Othman, and F M Kabole contributed to the implementation of the trial, design of data collection instruments, surveillance systems, and clinical care of patients.

Conflict of interest statement:

We declare that we have no conflict of interest

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