BMJ Open

Effect of zinc added to a daily small-quantity lipid-based nutrient supplement on diarrhoea, malaria, fever and respiratory infections in young children in rural Burkina Faso: a cluster-randomised trial

Jérôme W Somé,[1,2] Souheila Abbeddou,[2] Elizabeth Yakes Jimenez,[3] Sonja Y Hess,[2] Zinéwendé P Ouédraogo,[1] Rosemonde M Guissou,[1] Stephen A Vosti,[4] Jean-Bosco Ouédraogo,[1] Kenneth H Brown[2,5]

To cite: Somé JW, Abbeddou S, Yakes Jimenez E, *et al*. Effect of zinc added to a daily small-quantity lipid-based nutrient supplement on diarrhoea, malaria, fever and respiratory infections in young children in rural Burkina Faso: a cluster-randomised trial. *BMJ Open* 2015;**5**:e007828. doi:10.1136/bmjopen-2015-007828

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2015-007828).

Received 29 January 2015
Revised 6 July 2015
Accepted 16 July 2015

For numbered affiliations see end of article.

Correspondence to
Dr Sonja Y Hess;
syhess@ucdavis.edu

ABSTRACT

Objective: Preventive zinc supplementation in the form of tablets or syrup reduces the incidence of diarrhoea and acute lower respiratory tract infections (RTI), but its effect on malaria is inconsistent. When zinc is administered with other micronutrients or foods, its effect is also uncertain. We assessed the effects of different amounts and sources of zinc on the frequency of diarrhoea, malaria, fever and RTI in young children.

Design, setting and populations: This community-based, double-blind, placebo-controlled, cluster-randomised trial of 2435 children 9 months of age was carried out between April 2010 and July 2012 in rural southwestern Burkina Faso.

Interventions: Participants were randomly assigned at the concession level to receive daily 1 of 4 interventions for 9 months: (1) 20 g small-quantity lipid-based nutrient supplement (SQ-LNS) without zinc and placebo tablet, (2) 20 g SQ-LNS with 5 mg zinc and placebo tablet, (3) 20 g SQ-LNS with 10 mg zinc and placebo tablet or (4) 20 g SQ-LNS without zinc and 5 mg zinc tablet. Participants were visited weekly in their homes for morbidity surveillance for 9 months, and those with uncomplicated diarrhoea and malaria received treatment from the study field workers in the community.

Main outcomes: Incidence and longitudinal prevalence of diarrhoea, malaria, fever, and lower and upper RTI by intervention group.

Results: The incidence of diarrhoea, malaria and fever was 1.10 (±1.03 SD), 0.61 (±0.66 SD) and 1.49 (±1.12 SD) episodes per 100 child-days at risk, respectively, and did not differ by intervention group (p=0.589, p=0.856 and p=0.830, respectively). The longitudinal prevalence of acute lower RTI (0.1%; 95% IC 0.1–0.2%) and of upper RTI (7.8%; 95% IC 7.1–8.4%) did not differ among groups (p=0.234 and p=0.501, respectively).

Conclusions: Inclusion of 5 or 10 mg zinc in SQ-LNS and provision of 5 mg zinc dispersible tablet along with SQ-LNS had no impact on the incidence of diarrhoea, malaria and fever or the longitudinal prevalence of RTI compared with SQ-LNS without zinc in this population.

Trial registration number: NCT00944281.

Strengths and limitations of this study

- The strengths of the study include the double-masked randomised design and the rigorous quality control of the morbidity data collection with weekly supervision and regular retraining of the data collection team.
- The continuous active surveillance with a 7-day recall period minimises the variance.
- For ethical reasons, we provided morbidity treatment for all children, which may have altered the cumulative morbidity that they would have otherwise experienced and may have limited our ability to determine how zinc would have affected the health and morbidity of these children in the absence of such treatment.

INTRODUCTION

Undernutrition increases the risk and severity of diarrhoea and pneumonia, and accounts for approximately 45% of all child deaths.[1] A recent systematic review identified numerous effective interventions for reducing malnutrition and child deaths, including preventive zinc supplementation in populations at risk of zinc deficiency.[2] Research indicates that zinc supplementation reduces the incidence and severity of diarrhoea and acute lower respiratory infections in children,[3–5] but there is less certainty about the effects of preventive zinc supplementation on other types of infections, such

as malaria. The few trials that have been conducted to assess the impact of preventive zinc supplementation on malaria have had contradictory results.[6–10] The mechanism by which zinc modulates susceptibility to infections is uncertain, but is hypothesised to be due to its effects on different components of the immune system.[11]

There is also uncertainty about the optimal way to deliver additional zinc to children. Preventive zinc supplementation has been shown to be effective when delivered alone in the form of a tablet or syrup, but not when the supplement contained iron along with zinc.[12] Moreover, when zinc is provided with foods such as complementary foods or home fortification products mixed with foods (micronutrient powders (MNPs), lipid-based nutrient supplements), its effect on infectious morbidity is uncertain.[13 14]

Small-quantity lipid-based nutrient supplements (SQ-LNS) are a promising home fortification strategy to improve the micronutrient quality of children's diets.[15–17] SQ-LNS is a dietary supplement containing peanut paste, milk protein, essential fatty acids and a range of vitamins and minerals. None of the three published studies that investigated the impact of SQ-LNS on morbidity found a beneficial impact on diarrhoea.[15 18 19] This may be due to the fact that the zinc content of SQ-LNS was too low, the zinc was not well absorbed and/or the studies' sample sizes were inadequate.

In the International Lipid-based Nutrient Supplement-Zinc (iLiNS-Zinc) study, we provided varying amounts of zinc to children from 9 to 18 months of age via SQ-LNS or dispersible tablets, and we assessed incidence and longitudinal prevalence of diarrhoea, malaria, fever and respiratory tract infections during the same time period. Our objective was to determine the optimal dose of zinc to include in SQ-LNS for reducing infectious disease burden. We hypothesised that young Burkinabe children at risk of zinc deficiency who received either 5 or 10 mg zinc per day in SQ-LNS provided with meals, or a 5 mg zinc tablet per day provided between meals (positive control) would have a decreased incidence and longitudinal prevalence of diarrhoea, malaria, fever and respiratory tract infections compared with children who received SQ-LNS without added zinc and a placebo tablet (negative control). Cluster randomisation at the level of concession (ie, extended family compound) was chosen to reduce the risk of cross-contamination within the family compound through food sharing.

METHODS

Study design, site and population

The morbidity results reported in the current paper are from the iLiNS-Zinc study, a community-based, double-blind, placebo-controlled, cluster-randomised trial that took place between April 2010 and July 2012 in the Dandé health district in southwestern Burkina Faso. This region has a high prevalence of stunting (31.8%) and underweight (19.3%) among young children,[20] poor food security and holoendemic malaria transmission.[21] The study design has been described in detail by Hess *et al*.[21a] The study was registered with the US National Institutes of Health as a clinical trial (http://www.ClinicalTrials.gov; NCT00944281).

Randomisation

A total of 34 villages were selected for inclusion in the study based on their accessibility during the rainy season. Target villages were stratified by health clinic affiliation, average population size, and distance from the paved road and Bobo-Dioulasso, and assigned to the intervention cohort or the non-intervention cohort. Because morbidity was not assessed in the non-intervention cohort, this paper will focus just on the intervention cohort, which consisted of 25 villages. A statistician from the University of California Davis, who was blinded to the intervention groups, generated a random allocation sequence at the level of the concession (extended family compound) using SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA) to assign eligible children in the intervention cohort to one of four intervention groups. Every concession had a 1/8 chance of receiving one of the eight colour codes (two colours for each group to reinforce the blinding). During the trial, all participants, field staff, study statistician and investigators were blinded to the intervention groups.

Eligibility, enrolment and intervention

Potentially eligible children were identified by two censuses at a 1-year interval (November–December 2009 and 2010) in participating communities. Children were eligible if they were 8.80–9.99 months old, a permanent resident of Dandé health district, and their caregivers planned to be available during the study period and accepted home visits for data collection. Children were excluded when they had haemoglobin (Hb) concentration <50 g/L, weight-for-length <70% of the National Center of Health Statistics (NCHS) reference median,[22] bipedal oedema, other severe illness requiring hospital referral, a congenital abnormality or chronic medical condition, allergy towards peanuts or history of anaphylaxis or serious allergic reactions to any substance requiring emergency medical care, or were concurrently participating in any other clinical trial. Written informed consent was obtained from one of the child's primary caregivers. If the caregiver was illiterate, an impartial witness who was present during the consent process confirmed by co-signing that the information in the consent document was accurately explained to the participant, and that consent was freely given. During the enrolment visit, length and weight were measured, as described below. All children were screened for malaria parasites using a rapid diagnostic test (RDT, histidine-rich protein II; SD BIOLINE Malaria Ag P.F/Pan, Standard Diagnostics, INC, Kyonggi-do, Korea). If the RDT was positive, the child received antimalarial treatment (amodiaquine-artesunate, 1 tablet/day for 3 days) and

an antipyretic (paracetamol, 1/2 tablet × 3/day for 3 days). In case of fever with negative RDT, an antipyretic was provided for 3 days. Children with reported diarrhoea at the time of enrolment were treated with oral rehydration salts (ORS: 1 sachet/day for 4 days). Hb concentration was measured by Hemocue (Hemocue 201+, HemoCue AB, Ängelholm, Sweden). Children with Hb <80 g/L received iron supplements (ferrous sulfate, 2–6 mg iron/kg body weight/day, depending on anaemia severity) for 30 days and an anthelminthic (200 mg mebendazole/day) for 3 days. After being enrolled, participants in the intervention cohort were assigned to receive one of four interventions from 9 to 18 months of age: (1) SQ-LNS without zinc and placebo tablet (LNS-Zn0), (2) SQ-LNS with 5 mg zinc and placebo tablet (LNS-Zn5), (3) SQ-LNS with 10 mg zinc and placebo tablet (LNS-Zn10) or (4) SQ-LNS without zinc and 5 mg zinc tablet (LNS-TabZn5). Eligible twins were both enrolled in the study and received the same intervention and follow-up; however, only one randomly selected twin was included in the data analysis.

SQ-LNS, zinc and placebo tablets were produced by Nutriset SAS (Malaunay, France). All SQ-LNS products had the same appearance, aroma and flavour, and the zinc and placebo dispersible tablets were identical in appearance and flavour. The composition of SQ-LNS was the same for the four intervention formulations except for their zinc content. One sachet of 20 g SQ-LNS provided 118 kcal, 6 mg of iron, 5 or 10 mg added zinc for LNS-Zn5 and LNS-Zn10, respectively, and 19 other micronutrients.[17] The zinc tablet provided during this study is the same dispersible tablet provided by UNICEF and used in programmes for diarrhoea treatment in many countries, except the zinc content was 5 mg per tablet, provided as zinc sulfate. Caregivers were instructed on how to administer the study supplements and were advised to continue breast feeding and to feed diverse local foods. Caregivers were also instructed to administer 20 g SQ-LNS per day in two separate servings, preferably mixed in a small portion of the child's meal, and to give the dispersible tablet once a day at least 30 min away from meals and SQ-LNS. The latter instruction was provided to optimise zinc absorption.

Supplement distribution and community-based morbidity surveillance

From 9 to 18 months, children were visited weekly by trained field data collectors. During the first part of the study, the data collectors provided one plastic cup of 140 g of SQ-LNS and a blister package containing eight dispersible tablets (zinc or placebo) each week. Later in the study, the cups were replaced by seven 20 g sachets of SQ-LNS. Adherence was assessed by obtaining information on SQ-LNS and tablet consumption, and collecting any remaining SQ-LNS and tablets and empty packages.[23]

Field data collectors used a structured questionnaire to collect a weekly morbidity history, including the child's general state, appetite, number of semiliquid/liquid stools, presence of blood or mucus in stools, vomiting, fever, signs of respiratory tract infections, and any treatment received by the child either from study staff members or outside the study. If the child had a reported fever during the previous 24 h, auricular temperature was measured, and an RDT and blood smear slide were performed. As a quality control measure, auricular temperature was also measured once per month for all children independent of the caregiver's report. In the case of reported diarrhoea, fever with a negative RDT and fever with a positive RDT, the child was treated according to the Burkina Faso national guideline, as described above. Children were referred to the nearest health clinic for any danger signs (convulsions, lethargy or coma, persistent vomiting or inability to eat or drink), diarrhoea and malaria with complications, suspicion of lower respiratory tract infection, and any other symptoms requiring medical attention. Field data collectors resided in their assigned village, so that caregivers could seek treatment for the child outside of the regularly scheduled visit day. Field data collectors who were approached for unscheduled evaluations followed the same procedures outlined above.

On average, each field data collector was assigned to monitor 86±41 children during the entire study period. The 25 data collectors were supervised on a weekly basis by field supervisors. The work of the morbidity team was also continuously supervised by a trained nurse and two study physicians. Field data collectors and supervisors were retrained every 4–5 months to avoid any violation of the study protocol.

Anthropometric, health practices and socioeconomic status data collection

Anthropometric measurements were performed at baseline when children were 9 months old. All measurements were taken in duplicate. Weight was measured to the nearest 0.05 kg (Seca 383, Hamburg, Germany) and length to the nearest 0.1 cm (portable length board Seca 417, Hamburg, Germany). In case of disagreement between the first two measurements (greater than 0.1 kg for weight and 0.5 cm for length), a third measurement was performed. The average of the two closest values was used in the statistical analysis. Weight-for-length z-score (WLZ), weight-for-age z-score (WAZ) and length-for-age z-score (LAZ) were calculated using the SAS macros for the WHO Child Growth Standards.[24]

Data on feeding practices and child dietary intake were collected at baseline using a food frequency questionnaire that elicited information on consumption of predefined semisolid or solid food groups during the previous 24 h. Variables assessing breast feeding, meal frequency, dietary diversity and animal source food consumption were constructed based on the WHO indicators for assessing infant and young child feeding practices.[25]

Demographic and socioeconomic data were collected within 2 weeks after enrolment. Data were obtained on maternal education and marital status, Household Food Insecurity Access Scale (HFIAS),[26] number of children under 5 years in the household, and livestock possession and housing quality, as described in more detail by Hess *et al*.[27]

During monthly interviews, the caregiver was asked whether the participating child slept under a mosquito net the night preceding the visit, and whether the child received a high-dose vitamin A capsule during the preceding month. Photos of vitamin A supplements were shown to the caregiver to help differentiate between high-dose vitamin A supplements and the poliovirus oral vaccine.

Sample size

The longitudinal prevalences of diarrhoea and malaria were the primary outcomes. A total sample size of 2332 participants (583 per group) was needed to detect (with a significance of $p<0.05$ and power >0.80) ≥20% reduction in diarrhoea prevalence and malaria prevalence among the four groups, assuming an attrition rate of 15%. The expected effect sizes (0.22 SDs) were based on effects observed in previous zinc supplementation trials.[4 6 7 21 28] A total of 2435 children were enrolled in the study and 2364 of them were included in the final analyses after excluding participants with less than 30 days of morbidity observations.

Statistical analysis

Morbidity definitions

Diarrhoea was defined as caregiver report of three or more liquid or semiliquid stools during a 24 h period. An episode of diarrhoea was defined as the period starting the day the child first had diarrhoea following a diarrhoea-free period of 2 days, and ending on the last day the child had diarrhoea that was followed by ≥2 days without diarrhoea. The episode was considered to be severe when associated with observed signs of dehydration, reported presence of faecal blood, reported presence of six or more liquid or semi-liquid stools in 24 h, or when the episode lasted ≥14 days.

Fever was defined as: (1) any reported fever by the caregiver, whether or not the fever was confirmed by measured temperature during the last 24 h; or (2) any elevated measured auricular temperature (≥37.5°C). An episode of fever was defined as the period starting the day the child first had fever following a fever-free period of 2 days, and ending on the last day the child had fever that was followed by ≥2 days without fever. The episode of fever was considered to be unrelated to malaria (and classified as non-malaria fever) when there was no positive RDT for any day of the episode and within 2 days of the episode.

After enrolment, malaria was defined as the presence of reported or confirmed fever during the 24 h preceding the morbidity visit, associated with a positive RDT. A malaria episode was defined as the presence of a new episode of fever and positive malaria RDT obtained 21 days after a previously treated malaria episode. An episode of malaria was considered severe when it was accompanied by seizures, unconsciousness or respiratory distress (presence of wheezing/stridor or chest in-drawing).

Acute lower respiratory illness (ALRI) was defined as any episode in which the caregiver reported cough with respiratory difficulties (wheezing/stridor or chest in-drawing). An episode of ALRI ended on the last day the child had ALRI that was followed by at least 3 days free of respiratory distress.

Acute upper respiratory illness (AURI) was defined as any episode in which the caregiver reported cough and a purulent nasal discharge. An episode of AURI ended on the last day the child had AURI that was followed by at least 7 days free of purulent nasal discharge.

Incidence was defined as the number of new episodes of a disease per 100 days at risk and longitudinal prevalence as the per cent of total days of observation (or 'recalled' days) on which the disease was present (ie, the numerator is the total number of days with a disease and the denominator is the total number of days of observation). In the case of malaria, for each episode, the 21 days following the diagnosis of malaria were removed from the total days at risk.

Data quality, cleaning and statistical analysis

All data collection forms were checked for data quality (completeness, consistency, etc) by field supervisors and quality control agents. Data were double entered using EpiData V.3.1 (EpiData Association, Odense, Denmark) and the data sets were reviewed and validated on a weekly basis before appending to the previous cumulated database. Project coordinators routinely reviewed the data sets for errors (eg, study identification number, date of visit, group assignment, inconsistent variables, biologically implausible values and missing values) using Stata V.11.2 (StataCorp, Texas, USA) syntaxes. Original data collection forms were used for correction in cases of data entry errors identified by the coordinators. A statistical analysis plan was written by the study investigators and published to the project website (http://www.ilins.org) prior to the start of data analysis. The investigators remained blinded until consensus on primary conclusions was reached. Data analyses were completed using SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA).

Descriptive analysis was performed for baseline characteristics. Weighted means were calculated by weighting the mean number of illness days and prevalence by the total number of observation days, and by weighting the mean number of episodes and incidence rates by the total number of days at risk of a specific illness. The incidence or prevalence in the four intervention groups was compared by using binomial logistic regression and the events/trials syntax for the response

variable (SAS GLIMMIX procedure), controlling for baseline characteristics and allowing for overdispersion. The following covariates were included in the different models: participant's sex, baseline LAZ and WLZ (continuous), baseline Hb (continuous, only for malaria outcomes), iron supplementation at baseline (provision or not), and feeding practice indicators (child meets minimum requirement or not, only for diarrhoea outcomes); maternal education (no education, no formal education or <1 year formal education, ≥1 year formal education) and marital status/rank (sole wife in household, first wife in a polygamous household, and second wife or higher in a polygamous household), number of children under 5 years in the household (≤1 child, 2 children and ≥3 children); household food insecurity access score adjusted for season (season-adjusted HFIAS, quartiles), proxy of hygiene and water quality (quartiles), household livestock possession index (quartiles) and month/year of enrolment. Continuous variables were used when possible (normally distributed), and were categorised according to international standards if available (eg, WHO on infant and child feeding practices[25]), were constructed based on the study setting context (eg, maternal education), or were categorised into quartiles when other transformations were not useful. Because randomisation was carried out at the concession level, all analyses included random effects of concession. Pairwise comparisons between groups were carried out with a Tukey-Kramer adjustment to control for overall type I error.

A set of effect modifiers (sex, baseline continuous WLZ, baseline continuous and categorical (<1.5 or ≥1.5 SD[29]) LAZ, days at risk of illness by type of illness, maternal education and marital status (categorised as above), month/year of enrolment, seasonal adjusted HFIAS score (quartiles), housing quality (quartiles, for diarrhoea only), and iron supplementation at enrolment) were selected a priori and were assessed individually in the models with all the covariates, by including the potential effect modifier as a main effect and in an interaction with the intervention group variable. Stratified analyses were performed to assess the nature of the interaction when the interaction term was significant at the 5% level.

Final morbidity analyses included only children with at least 30 days of morbidity observations. However, in a sensitivity analysis, the inclusion of all available data did not affect the results (see online supplemental table S1). Data are presented as means±SD, unless otherwise noted. p Values <0.05 were considered statistically significant.

RESULTS

A total of 3402 children were initially contacted, of whom 3220 eligible children of consenting families were enrolled in the study. Of these, 2435 children resided in randomly assigned intervention communities and 785 in non-intervention communities. The 2435 children in the intervention cohort were randomly assigned to one of the four intervention groups and were followed weekly for morbidity assessment (figure 1). Caregivers of 97% of the participating children provided information on at least 30 days of morbidity surveillance, and 78% of the caregivers provided information for at least 35 weeks. The 71 children who were excluded from the final analyses because they provided less than 30 days of morbidity observations did not differ at baseline from those included in the analysis (data not shown). There were no differences in participation or reporting rates among the four intervention groups.

The mean age of participants at enrolment was 9.4 months (range 8.7–10.7). More than half of the mothers (58%) did not receive any kind of education, and only 11% of them completed at least 1 year of formal education. The median number of children under 5 years per household was 2.0 (IQR=1–3) with 34% of households having at least one other child less than 5 years of age in addition to the study participant. The median seasonally adjusted HFIAS score was 1.50 (IQR=0.69–4.50) on a scale of 0–27, with higher score indicating more food insecurity. The malaria RDT was positive for ≈59% of the children at enrolment. Almost all of the children (91%) were anaemic based on Hb cut-off <110 g/L. Iron supplementation was provided to 26% of children at the enrolment visit, along with antihelminthic treatment. At baseline, ≈3% of children were severely wasted (WLZ≤−3 SD, according to the WHO growth standard), and ≈13% were moderately wasted (−3 SD≤WLZ<−2 SD). Approximately 5% of children were severely stunted (LAZ≤−3 SD) and ≈18% were moderately stunted (−3 SD≤LAZ<−2 SD). Baseline characteristics of the participants are shown by intervention group in table 1.

The median number of observation days for all children was 260 days (IQR=244–271). The overall daily reported adherence for SQ-LNS and the tablets was very high and did not differ among intervention groups. More than 80% of children reportedly consumed the SQ-LNS and tablets on at least 95% of the study days.

Caregivers were questioned once monthly about whether their child slept under a mosquito net the night before the field worker's visit, and the caregivers responded positively on seven of the nine possible occasions (IQR=5–8 times). Only 1.5% of caregivers (n=35) reported that the child did not use a mosquito net at all during the entire study period. There was no difference in mosquito net use by intervention group. About 58% of caregivers stated that their child received at least one vitamin A supplement during the study period, with no difference between groups.

The median number of days at risk for diarrhoea, fever, malaria, and acute upper and lower respiratory tract infections (AURI and ALRI) were 250 (IQR=230–260), 248 (IQR=228–258), 215 (IQR=186–236), 235 (IQR=192–254) and 261 (IQR=246–270), respectively,

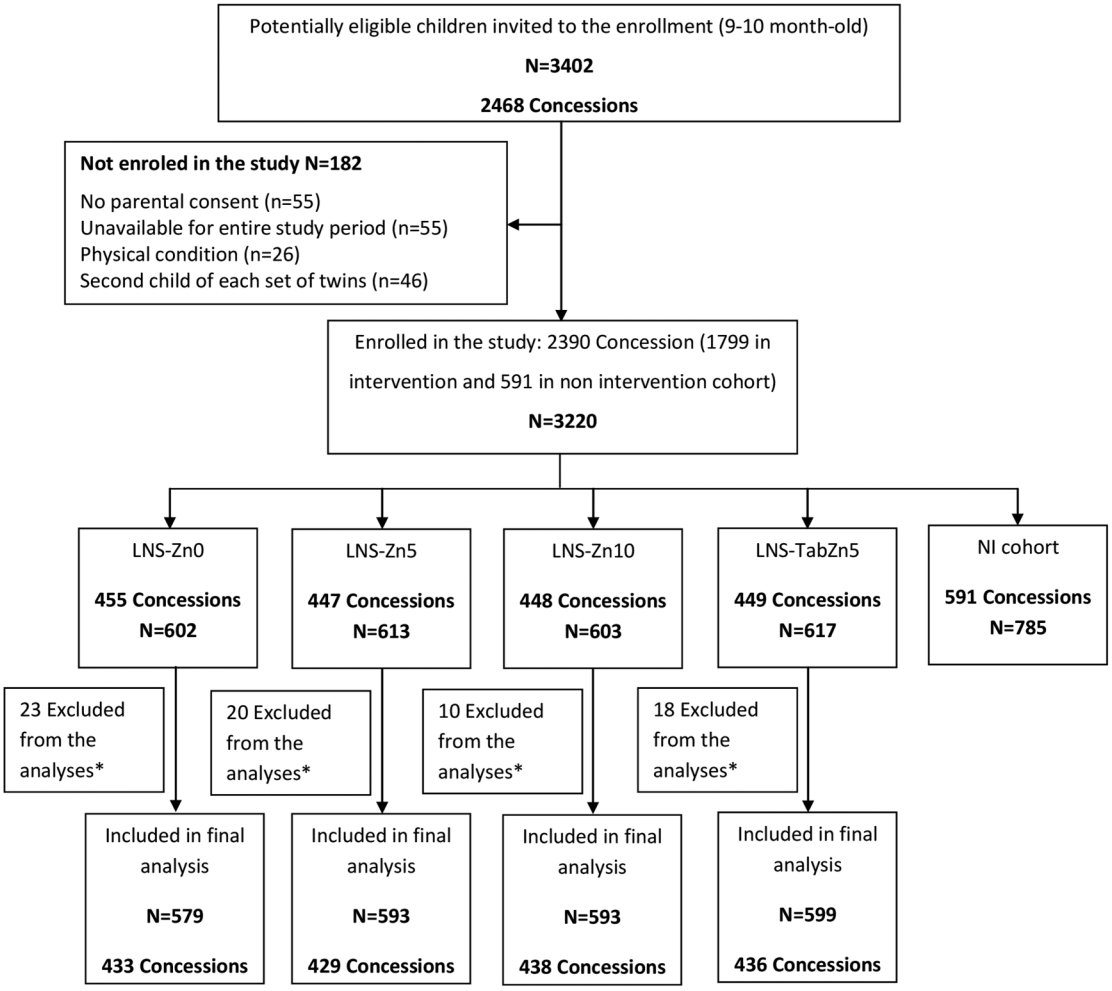

Figure 1 Flow diagram for the study participants from the initial census to the analysis of the morbidity outcomes. *Excluded from analyses because participants provided <30 days of morbidity surveillance. LNS-Zn0, SQ-LNS without zinc and placebo tablet; LNS-Zn5, SQ-LNS with 5 mg zinc and placebo tablet; LNS-Zn10, SQ-LNS with 10 mg zinc and placebo tablet; LNS-TabZn5, SQ-LNS without zinc and 5 mg zinc tablet; NI, non-intervention.

and were not significantly different among intervention groups.

The longitudinal prevalence of diarrhoea was 3.1% (95% CI 2.9% to 3.2%), and the incidence was 1.10 ±1.03 episodes per 100 child-days which is equivalent to 4.01±3.76 episodes per child-year. Diarrhoea morbidity did not differ by intervention group (table 2), even when more stringent criteria were used, such as higher stool frequency, prolonged illness or associated complications. About 17.5% of the participants did not report any episodes of diarrhoea during the 9-month observation period. Thirty-nine per cent of children with diarrhoea received ORS treatment, as per the study protocol, and there were no differences in treatment rates by study group.

The longitudinal prevalence of malaria was 1.5% (95% CI 1.4% to 1.6%) with children having on average 3.8±4.1 days of malaria during the study period. The incidence of malaria was 0.61±0.66 episodes per 100 child-days (equivalent to 2.23±2.40 episodes per child-year) and was not different among intervention groups. Among the positive RDTs, *Plasmodium falciparum* was present in 91% of cases. About 31% of the participants did not experience any episodes of malaria during the entire observation period. Malaria treatment was provided per study protocol to almost all children with malaria (99.0%). The proportion of treated episodes of malaria did not differ by group (table 2). The average duration of malaria episodes was not statistically different among intervention groups: 2.86, 2.99, 2.95 and 2.99 days (p=0.683), respectively, for LNS-Zn0, LNS-Zn5, LNS-Zn10 and LNS-TabZn5. During the 9-month follow-up period, there were only 16 cases of severe malaria with no difference by intervention group.

The longitudinal prevalence of fever was 3.5% (95% CI 3.4% to 3.7%). On average, participants had 8.5 ±7.2 days with fever and 8% of children did not experience any days with fever. Forty-five per cent of days with fever were associated with malaria. The incidence of fever was 1.49±1.12 episodes per 100 child-days (equivalent to 5.44±4.09 episodes per child-year) with no difference among intervention groups. The average duration

Table 1 Baseline characteristics of study participants by intervention group

	LNS-Zn0	LNS-Zn5	LNS-Zn10	LNS-TabZn5
N	602	613	603	617
Child characteristics				
Sex (% male)	50.7	48.8	53.1	49.3
Mean age (month)	9.4±0.3	9.4±0.4	9.4±0.3	9.4±0.4
Mean LAZ	−1.21±1.07	−1.20±1.11	−1.32±1.07	−1.12±1.10
Mean WLZ	−0.96±1.06	−0.95±1.08	−1.09±0.99	−0.89±1.06
% (n) Stunting (LAZ <−2 SD)*	23.1 (139)	22.1 (135)	26.2 (158)	20.2 (124)
% (n) Wasting (WLZ <−2 SD)*	16.6 (100)	15.4 (94)	18.4 (111)	14.3 (88)
% (n) Underweight (WAZ <−2 SD)*	26.6 (160)	29.4 (180)	34.0 (205)	26.4 (163)
% RDT positive	61.3	58.4	61.0	56. 9
Mean haemoglobin (g/L)	90±15	90±16	89±15	90±15
% iron supplementation	24.7	25.3	26.5	26.4
% (n)≥Minimum meal frequency in previous 24 h†‡	35.8 (215)	33.8 (207)	36.3 (219)	32.9 (203)
% (n)≥Minimum dietary diversity in previous 24 h§	10.0 (60)	12.6 (77)	13.1 (79)	12.8 (79)
% (n)≥1 animal source food in previous 24 h¶	21.5 (129)	24.1 (148)	22.2 (134)	23.3 (144)
Maternal characteristics				
Per cent of mothers with no education	60.8	56.2	56.3	57.7
Per cent of sole wife of household	57.5	50.1	57.1	60.8
Household characteristics (N)	552	555	549	559
Median of number children ≤5 years	2.0 (IQR=1–3)	2.0 (IQR=1–3)	2.0 (IQR=1–2)	2.0 (IQR=1–2)
Median seasonally adjusted HFIAS score	1.50 (IQR=0.69–4.69)	1.50 (IQR=0.69–4.69)	1.50 (IQR=0.69–4.80)	1.50 (IQR=0.69–3.80)
Housing quality index	−0.01±1.00	0.11±0.99	−0.03 2±0.98	0.10±1.04
Livestock index (TLU)	4.76±7.81	4.78±8.09	4.46±6.59	4.89±12.72

Results shown are mean±SD or percentage and median with IQR.
Housing quality index constructed based on following characteristics: drinking water supply, sanitation facilities, wall material, flooring material and roofing material, which were combined into an asset using (with a mean of zero and a SD of one) principal component analysis.
*WHO Child Growth Standards.[24]
†Minimum meal frequency during the previous 24 h is 3 meals/snacks if the child is still breast fed or 4 meals/snacks if the child is not breast fed.[25]
‡The collection of the variable started after the beginning of the study, therefore information on 195 participants is missing.
§Minimum food group diversity during the previous 24 h is consumption of four or more food groups out of seven.[25]
¶Consumption of one or more animal source food during the previous 24 h.
HFIAS, Household Food Insecurity Access Scale; LAZ, length-for-age z-score; LNS-Zn0, SQ-LNS without zinc and placebo tablet; LNS-Zn5, SQ-LNS with 5 mg zinc and placebo tablet; LNS-Zn10, SQ-LNS with 10 mg zinc and placebo tablet; LNS-TabZn5, SQ-LNS without zinc and 5 mg zinc tablet; SQ-LNS, small-quantity lipid-based nutrient supplement; RDT, rapid diagnostic test; TLU, tropical livestock unit; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score.

of the episodes of fever was not statistically different by groups: 2.47, 2.50, 2.49 and 2.53 days (p=0.733), respectively, for LNS-Zn0, LNS-Zn5, LNS-Zn10 and LNS-TabZn5. Fever treatment was provided for 72.3% of fever episodes, and the proportion of treated episodes of fever did not differ among groups. The longitudinal prevalence and incidence of non-malaria fever were 2.02% (95% CI 1.92% to 2.12%) and 0.95±0.99 episodes per 100 child-days, respectively, and were not different by intervention group (table 2).

The mean number of days with AURI and ALRI were 19.6±32.3 and 0.3±3.2, respectively. Almost 36% of children (n=847) had no episodes of AURI reported and 97% (n=2284) had no episodes of ALRI. The longitudinal prevalence for AURI was 7.8% (95% CI 7.1% to 8.4%) and for ALRI 0.1% (95% CI 0.1% to 0.2%). There were no differences in any of the respiratory morbidity indicators by intervention group (table 2).

There were no significant interactions between zinc intervention group and the different predetermined effect modifiers for the incidence of diarrhoea, malaria or fever.

Seventy severe adverse events (SAEs), defined as hospitalisations or deaths, occurred during the 9-month follow-up period. These SAEs did not differ significantly by intervention group (p=0.497). Of the 2435 children enrolled in the intervention cohort, 33 died during the follow-up period: 9 (1.50%), 2 (0.33%), 10 (1.66%) and 12 (1.94%) participants in the LNS-Zn0, LNS-Zn5, LNS-Zn10 and LNS-TabZn5, respectively. The main suspected causes of death were severe malaria, gastroenteritis and respiratory infections.

DISCUSSION

The present dose–response trial aimed to determine the optimal amount of zinc to include in SQ-LNS for the prevention of common childhood infections. We found no impact of adding either 5 or 10 mg zinc to the daily portion of SQ-LNS, or of providing 5 mg zinc/day as a

Table 2 Number of episodes, incidence and longitudinal prevalence of diarrhoea, fever, malaria and respiratory tract infections in young children during 9 months of observation by intervention group*

	LNS-Zn0 n=579	LNS-Zn5 n=593	LNS-Zn10 n=593	LNS-TabZn5 n=599	p Value†	p Value‡
Total number of child-days for diarrhoea	134 827	136 531	136 630	138 275		
Number of episodes of diarrhea§	2.61±2.27	2.67±2.27	2.51±2.15	2.52±2.26	0.473	0.587
Incidence of diarrhoea (episodes/100 child-days at risk)§	1.11±1.05	1.14±1.05	1.06±0.98	1.08±1.02	0.580	0.589
Number of episodes of severe diarrhoea§	0.55±0.94	0.64±1.01	0.61±0.96	0.57±0.96	0.742	0.509
Incidence of severe diarrhoea (episodes/100 child-days at risk)§	0.24±0.42	0.27±0.46	0.26±0.41	0.25±0.45	0.744	0.511
Number of diarrhoea episodes treated with ORS§	0.97±1.12	0.96±1.22	0.98±1.16	0.90±1.17	0.611	0.723
Per cent of diarrhoea episodes treated with ORS§	39.7 (36.4 to 42.9)	36.4 (33.4 to 39.5)	41.3 (38.0 to 44.6)	37.6 (34.3 to 40.8)	0.355	0.418
Total number of child-days for fever	133 715	135 490	135 198	137 012		
Number of episodes of fever¶	3.57±2.46	3.44±2.54	3.49±2.43	3.42±2.30	0.472	0.728
Incidence of fever (episodes/100 child-days at risk)¶	1.53±1.16	1.48±1.19	1.48±1.10	1.46±1.04	0.787	0.830
Number episodes of fever treated with antipyretic and/or antimalaria¶	2.38±1.71	2.34±1.76	2.49±1.81	2.34±1.74	0.397	0.638
Per cent of fever episodes treated with antipyretic and/or antimalaria¶	70.9 (68.3 to 73.5)	71.8 (69.2 to 74.4)	74.3 (71.9 to 76.7)	72.1 (69.5 to 74.6)	0.063	0.091
Incidence of non-malaria fever (episodes/100 child-days at risk)¶	0.97±1.05	0.93±1.03	0.95±0.95	0.94±0.93	0.883	0.920
Longitudinal prevalence of non-malaria fever¶	2.06 (1.86 to 2.27)	1.96 (1.76 to 2.15)	2.05 (1.85 to 2.25)	2.00 (1.81 to 2.19)	0.814	0.713
Total number of child-days for malaria	117 513	119 467	119 156	121 395		
Number of malaria episodes**	1.32±1.14	1.30±1.19	1.27±1.10	1.24±1.12	0.615	0.872
Incidence of malaria (episodes/100 child-days at risk)**	0.63±0.65	0.62±0.70	0.61±0.63	0.59±0.65	0.762	0.856
Number of episodes of malaria treated with antimalaria**	1.31±1.13	1.29±1.19	1.26±1.09	1.21±1.11	0.544	0.803
Per cent of malaria episodes treated with antimalaria**	99.2 (98.5 to 99.9)	99.1 (98.4 to 99.9)	99.4 (98.9 to 99.8)	98.3 (97.2 to 99.4)	0.518	0.430
Number of days with AURI††	19.1±32.6	18.6±30.3	20.3±32.0	20.3±34.2	0.873	0.695
Longitudinal prevalence of AURI††	7.5 (6.3 to 8.7)	7.3 (6.2 to 8.4)	8.1 (6.9 to 9.3)	8.1 (6.7 to 9.4)	0.658	0.501
Number of days with ALRI††	0.3±2.4	0.5±4.9	0.3±2.1	0.3±2.3	0.650	0.451
Longitudinal prevalence of ALRI††	0.12 (0.01 to 0.23)	0.19 (0.03 to 0.34)	0.12 (0.04 to 0.19)	0.10 (0.03 to 0.18)	0.606	0.234

*Values are mean±SD for number of episodes, number of days of illness and incidence (episodes per 100 child-days at risk), and percentage (95% CI) for longitudinal prevalence. Values of incidence and longitudinal prevalence are weighted by the number of days at risk and number of days of observation, respectively. Incidence and longitudinal prevalence were compared by intervention group using binomial logistic regression. Linear mixed model was used for the group-wise comparisons of number of episodes and number of days of illness.
†Unadjusted p value (models allowed for overdispersion and included random effect of concession except for comparison of percentage of treated episodes in which models did not include effect of concession).
‡Adjusted p value (models included a set of covariates, and the random effect of concession and allowed for overdispersion).
§For diarrhoea, group-wise comparisons were performed controlling for child sex, baseline LAZ and WLZ, month and year of enrolment, number of days at risk of diarrhoea, maternal education and marital status, seasonally adjusted HFIAS score, housing quality index, livestock index, minimum meal frequency, minimum food group diversity and consumption of animal source foods at 9 months.
¶For fever, group-wise comparisons were performed controlling for child sex, baseline LAZ and WLZ, month and year of enrolment, number of days at risk of fever, maternal education and marital status, seasonally adjusted HFIAS score and iron supplementation.
**For malaria, group-wise comparisons were performed controlling for child sex, baseline LAZ and WLZ, baseline haemoglobin, month and year of enrolment, number of days at risk of malaria, maternal education and marital status and seasonally adjusted HFIAS score.
††For respiratory tract infections, group-wise comparisons were performed controlling for child sex, baseline LAZ and WLZ, month and year of enrolment, number of days of observation, maternal education and marital status, seasonally adjusted HFIAS score and iron supplementation.
AURI, acute upper respiratory illness; ALRI, acute lower respiratory illness; HFIAS, Household Food Insecurity Access Scale; LAZ, length-for-age z-score; LNS-Zn0, SQ-LNS without zinc and placebo tablet; LNS-Zn5, SQ-LNS with 5 mg zinc and placebo tablet; LNS-Zn10, SQ-LNS with 10 mg zinc and placebo tablet; LNS-TabZn5, SQ-LNS without zinc and 5 mg zinc tablet; ORS, oral rehydration salts; SQ-LNS, small-quantity lipid-based nutrient supplement; WLZ, weight-for-length z-score.

dispersible tablet on the incidence, longitudinal prevalence or duration of diarrhoea, malaria, fever or respiratory tract infections in children 9–18 months of age, compared with SQ-LNS without zinc. These results differ from the findings of previous community-based trials of preventive zinc supplementation. In particular, three meta-analyses of preventive zinc supplementation, in which zinc was given in form of a tablet or syrup, reported that diarrhoea incidence was reduced by 13–20%, and acute lower respiratory tract infection incidence was reduced by 8–19%, compared with a control group.[4 5 30]

Possible explanations for the lack of any observed effects of zinc on morbidity outcomes in the present study are: (1) the population was not zinc deficient, (2) the supplemental zinc was poorly absorbed or utilised, (3) the supplements were not consumed in sufficient amounts or (4) other components of the supplement interfered with the beneficial effects of zinc.

With regard to the first possibility, we have previously reported that 35.2% of the children had initial plasma zinc concentrations <65 mg/L,[27] and there was a high prevalence of stunting, so the study population does, indeed, seem to have a high risk of zinc deficiency.

It is well known that zinc absorption from cereal-based diets is substantially less than from dispersible tablets or liquid supplements, in part due to the phytate content of the mixed diets.[31 32] Although the phytate content of the SQ-LNS used in the present study is very low (phytate:zinc molar ratio <1),[17 33] the phytate:zinc ratio may be higher when SQ-LNS is mixed with foods. In the study site, complementary foods for infants and young children are mainly cereal-based, so this may have reduced zinc uptake. However, we have previously found that adding zinc fortificants to cereal-based diets increases net zinc absorption,[34 35] so there should have been progressively greater zinc uptake when higher amounts were added to SQ-LNS. If this had occurred, we would have expected to see the strongest protective effect in the LNS-Zn10 group. Additionally, in a subgroup of participants (n=192) at 11 and 16 months of age, SQ-LNS was observed given alone (as a snack) in 60% and 86% of the observed servings, respectively, so possible interference of the diet with zinc uptake would be less likely in these cases.[23]

Another possibility is that the postabsorptive metabolism of zinc differs when it is provided with food rather than as a supplement given between meals. For example, previous studies have found that providing zinc in food produces a lower response in plasma zinc concentration than when additional zinc is provided as a supplement.[36–38] However, in the present study, we also failed to detect a significant rise in plasma zinc concentration in the positive control group that received additional zinc in the form of a dispersible tablet, which has been previously shown to have a substantial impact on plasma zinc concentration when administration was directly observed in a very similar study population in neighbouring communities in Burkina Faso.[39] This suggests that adherence to the study supplements might have been insufficient to produce a functional response in zinc status in the present study, despite the high reported adherence rate, as described previously.[23]

One recent meta-analysis of the effect of preventive zinc supplementation concluded that the beneficial effects of supplemental zinc for reducing diarrhoea incidence were not detectable when zinc was provided along with iron.[12] The SQ-LNS used in the present study contained 6 mg iron. Because all of the study groups received SQ-LNS containing iron, we cannot rule out the possibility that iron in the SQ-LNS undermined a potentially beneficial effect of zinc on diarrhoea. The current study results are similar to a recent report from Haiti, where providing 4 mg zinc daily in 20 g LNS to infants aged 6–11 months for 3 or 6 months had no effect on diarrhoea, respiratory infections and other morbidity outcomes, compared with a non-supplemented control group.[18] Similarly, a previous study in Peru found no effect of adding 3 mg zinc/day to a cereal porridge on diarrhoea, fever, and upper and lower respiratory infections in young children.[36]

Evidence for a preventive effect of zinc supplementation on malaria incidence is inconsistent. Only one study conducted in Papua New Guinea, using a 10 mg zinc tablet to supplement children aged 6–60 months, found a significant 38% reduction in microscopy-confirmed malaria-related visits to a health facility.[9] A second study carried out earlier in the Gambia, in which children aged 0.6–2.3 years received a beverage fortified with 70 mg zinc or a placebo beverage twice weekly, found a trend towards fewer malaria episodes based on health clinic records.[6] Both studies reported a reduction in severe malaria episodes requiring a visit to a health facility. In the present study, we hypothesised that the weekly home visits to diagnose and treat malaria may have prevented severe malaria episodes requiring a visit to a health centre and possibly hospitalisation. A relatively recent study that was completed in Burkina Faso, providing both zinc and high-dose vitamin A supplements, found a 30% reduction in malaria episodes among children 6–72 months of age, but it was not possible to attribute this effect specifically to zinc.[21] In contrast, three other studies did not show any effect of zinc supplementation on malaria, similar to our study. Two of the latter studies, implemented in Burkina Faso and Peru, and using community-based assessment of malaria, found no effect of supplemental zinc, alone or in combination with iron, on malaria compared with no zinc.[7 8] The third study by Veenemans *et al*[10] assessed malaria through health clinic visits and did not find that the supplementation of zinc alone, or multinutrients with or without zinc, affected clinic-based confirmed malaria incidence in Tanzanian children aged 6–60 months compared with placebo. They also reported no effect on severe malaria episodes.

Recent studies of iron supplements and iron-containing MNPs found an increased incidence of diarrhoea and respiratory infections.[40–42] We could not assess the effect of iron in the present study because all intervention groups received iron-containing SQ-LNS. There was no evidence to suggest that the addition of 5 or 10 mg zinc to SQ-LNS produced adverse effects. There was no increase in the incidence, prevalence or duration of any of the diseases of interest in the LNS-Zn5 or LNS-Zn10 groups compared with the negative and positive control groups. However, the study was not powered to detect a potential difference in hospitalisation and mortality rates among intervention groups. Notably, the death rate was significantly lower for the intervention cohort (ie, the combined 4 intervention groups) compared with the non-intervention cohort.[27]

Several strengths of the current study are noteworthy. The morbidity surveillance was rigorously supervised, data collection forms were reviewed weekly and the data collection team was included in frequent refresher training. The data were double entered and edited methodically. Although more frequent morbidity surveillance (eg, 2–3 days recall) might have been preferable to minimise possible recall bias,[43 44] a recent analysis of morbidity surveillance found that a 7-day recall period had little bias with regard to comparing incidence rates among specific risk groups, and the mean square error was minimised with a recall period of approximately 7 days.[45] Another possible limitation of the study is the fact that we provided treatment for all children in the intervention cohort who were reported to have diarrhoea, fever or confirmed malaria, which may have reduced our ability to determine how zinc would have affected the children's risk of morbidity in the absence of such treatment. Moreover, it is conceivable that the presence of other nutrients in LNS reduced the ability to detect a specific additive effect of supplemental zinc.

CONCLUSION

Supplementation with 5 or 10 mg zinc added to SQ-LNS or with a 5 mg dispersible zinc tablet did not affect the incidence, longitudinal prevalence or duration of diarrhoea, fever, malaria and respiratory tract infection in Burkinabe children aged 9–18 months compared with children receiving SQ-LNS without any added zinc. Inadequate zinc absorption from SQ-LNS and insufficient adherence to the dispersible tablets are possible explanations for the absence of any detectable effects of additional zinc in the study population. SQ-LNS absorption studies are needed to evaluate the quantity of absorbed zinc when a child consumes SQ-LNS. Based on the results of the present study, it is not possible to determine the optimal amount of zinc to add to SQ-LNS, so current WHO guidelines on the zinc content of home fortification products for children should remain in effect until additional data become available from other dose–response trials.

Author affiliations
[1]Institut de Recherche en Sciences de la Santé/Direction Régionale de l'Ouest, Bobo-Dioulasso, Burkina Faso
[2]Program in International and Community Nutrition, Department of Nutrition, University of California, Davis, California, USA
[3]Departments of Individual, Family and Community Education, and Family and Community Medicine, University of New Mexico, Albuquerque, New Mexico, USA
[4]Department of Agricultural and Resource Economics, University of California, Davis, California, USA
[5]The Bill and Melinda Gates Foundation, Seattle, Washington, USA

Acknowledgements The authors thank the entire iLiNS-Zinc team (especially the morbidity surveillance team) in Burkina Faso and UC Davis. Special thanks go to Janet Peerson (University of California, Davis, USA) for assistance with programming and statistical analyses and the iLiNS Project Steering Committee (http://www.ilins.org) for technical support. Finally, they sincerely appreciate the support of the participating children and their parents, the local communities and the staff of the health district of Dandé.

Contributors KHB, SYH and J-BO were responsible for the design of the study. SA, EYJ, JWS, ZPO and RMG implemented the research and SYH, KHB, SAV and J-BO supervised data collection. JWS and SA completed the statistical analyses and JWS drafted the manuscript. SA, EYJ, SYH and KHB edited the manuscript. All authors read and approved the final manuscript.

Funding This article is based on research funded by a grant to the University of California, Davis from the Bill and Melinda Gates Foundation.

Disclaimer The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Ethics approval Institutional Review Board of Centre Muraz (Bobo-Dioulasso, Burkina Faso) and University of California, Davis (USA).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Black RE, Victora CG, Walker SP, *et al*. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013;382:427–51.
2. Bhutta ZA, Das JK, Rizvi A, *et al*. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet* 2013;382:452–77.
3. Bhutta ZA, Black RE, Brown KH, *et al*. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. *J Pediatr* 1999;135:689–97.
4. Brown KH, Peerson JM, Baker SK, *et al*. Preventive zinc supplementation among infants, preschoolers, and older prepubertal children. *Food Nutr Bull* 2009;30(Suppl 1):S12–40.
5. Mayo-Wilson E, Junior JA, Imdad A, *et al*. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. *Cochrane Database Syst Rev* 2014;5:CD009384.
6. Bates CJ, Evans PH, Dardenne M, *et al*. A trial of zinc supplementation in young rural Gambian children. *Br J Nutr* 1993;69:243–55.
7. Müller 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. *BMJ* 2001;322:1567.

8. Richard SA, Zavaleta N, Caulfield LE, *et al*. Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. *Am J Trop Med Hyg* 2006;75:126–32.
9. Shankar AH, Genton B, Baisor M, *et al*. The influence of zinc supplementation on morbidity due to Plasmodium falciparum: a randomized trial in preschool children in Papua New Guinea. *Am J Trop Med Hyg* 2000;62:663–9.
10. Veenemans J, Milligan P, Prentice AM, *et al*. Effect of supplementation with zinc and other micronutrients on malaria in Tanzanian children: a randomised trial. *PLoS Med* 2011;8:e1001125.
11. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr* 1998; 68(2 Suppl):447S–63S.
12. Mayo-Wilson E, Imdad A, Junior J, *et al*. Preventive zinc supplementation for children, and the effect of additional iron: a systematic review and meta-analysis. *BMJ Open* 2014;4:e004647.
13. Das JK, Salam RA, Kumar R, *et al*. Micronutrient fortification of food and its impact on woman and child health: a systematic review. *Syst Rev* 2013;2:67.
14. Eichler K, Wieser S, Ruthemann I, *et al*. Effects of micronutrient fortified milk and cereal food for infants and children: a systematic review. *BMC Public Health* 2012;12:506.
15. Adu-Afarwuah S, Lartey A, Brown KH, *et al*. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *Am J Clin Nutr* 2007;86:412–20.
16. Phuka JC, Maleta K, Thakwalakwa C, *et al*. Complementary feeding with fortified spread and incidence of severe stunting in 6- to 18-month-old rural Malawians. *Arch Pediatr Adolesc Med* 2008;162:619–26.
17. Arimond M, Zeilani M, Jungjohann S, *et al*. Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: experience from the International Lipid-Based Nutrient Supplements (iLiNS) Project. *Matern Child Nutr* Published Online First: 6 May 2013. doi: 10.1111/mcn.12049
18. Iannotti LL, Dulience SJ, Green J, *et al*. Linear growth increased in young children in an urban slum of Haiti: a randomized controlled trial of a lipid-based nutrient supplement. *Am J Clin Nutr* 2014;99:198–208.
19. Mangani C, Ashorn P, Maleta K, *et al*. Lipid-based nutrient supplements do not affect the risk of malaria or respiratory morbidity in 6- to 18-month-old Malawian children in a randomized controlled trial. *J Nutr* 2014;144:1835–42.
20. Institut National de la Statistique et de la Démographie et ICF International. *Enquête Démographique et de Santé et à Indicateurs Multiples du Burkina Faso 2010*. Calverton, MD, USA: INSD et ICF International, 2012.
21. Zeba AN, Sorgho H, Rouamba N, *et al*. Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: a randomized double blind trial. *Nutr J* 2008;7:7.

21a. Hess SY, Abbeddou S, Yakes Jimenez E, *et al*. Small-quantity lipid-based nutrient supplements, regardless of their zinc content, increase growth and reduce the prevalence of stunting and wasting in young Burkinabe children: a cluster-randomized trial. *PLoS One* 2015. 10.1371/journal.pone.0122242.

22. [No authors listed]. Use and interpretation of anthropometric indicators of nutritional status. WHO Working Group. *Bull World Health Organ* 1986;64:929–41.
23. Abbeddou S, Hess SY, Yakes Jimenez E, *et al*. Comparison of methods to assess adherence to small-quantity lipid-based nutrient supplements (SQ-LNS) and dispersible tablets among young Burkinabé children participating in a community-based intervention trial. *Matern Child Nutr* Published Online First: 17 Dec 2014. doi.10.1111/mcn.12162.
24. World Health Organization. *WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development*. Geneva: World Health Organization, 2006:336.
25. World Health Organization. *Indicators for assessing infant and young child feeding practices. Part 2 measurement*. Geneva: World Health Organization, 2010:91.
26. Coates J, Swindale A, Bilinsky P. *Household Food Insecurity Access Scale (HFIAS) for measurement of food access: indicator guide*. Washington DC: USAID, 2007.
27. Hess SY, Abbeddou S, Jimenez EY, *et al*. Small-quantity lipid-based nutrient supplements, regardless of their zinc content, increase growth and reduce the prevalence of stunting and wasting in young Burkinabe children: a cluster-randomized trial. *PLoS ONE* 2015;10: e0122242.
28. Brown KH, Peerson JM, Kimmons JE, *et al*. Options for achieving adequate intake from home-prepared complementary foods in low income countries. In: Black RE, Fleischer Michaelsen K, eds. *Public health issues in infant and child nutrition*. Philadelphia: Nestec Ltd., Vevey/Lippincott Williams & Wilkins, 2002:239–56.
29. Brown KH, Peerson JM, Rivera J, *et al*. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002;75:1062–71.
30. Yakoob MY, Theodoratou E, Jabeen A, *et al*. Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. *BMC Public Health* 2011;11(Suppl 3):S23.
31. Hambidge KM, Miller LV, Westcott JE, *et al*. Zinc bioavailability and homeostasis. *Am J Clin Nutr* 2010;91:1478S–83S.
32. Brown KH, Rivera JA, Bhutta Z, *et al*. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. *Food Nutr Bull* 2004;25(1 Suppl 2):S99–203.
33. Gibson RS, Bailey KB, Gibbs M, *et al*. A review of phytate, iron, zinc, and calcium concentrations in plant-based complementary foods used in low-income countries and implications for bioavailability. *Food Nutr Bull* 2010;31(Suppl 2):S134–46.
34. Hess SY, Brown KH. Impact of zinc fortification on zinc nutrition. *Food Nutr Bull* 2009;30(1 Suppl):S79–107.
35. Lopez de Romana D, Salazar M, Hambidge KM, *et al*. Longitudinal measurements of zinc absorption in Peruvian children consuming wheat products fortified with iron only or iron and 1 of 2 amounts of zinc. *Am J Clin Nutr* 2005;81:637–47.
36. Brown KH, Lopez de Romana D, Arsenault JE, *et al*. Comparison of the effects of zinc delivered in a fortified food or a liquid supplement on the growth, morbidity, and plasma zinc concentrations of young Peruvian children. *Am J Clin Nutr* 2007;85:538–47.
37. Aaron GJ, Ba Lo N, Hess SY, *et al*. Plasma zinc concentration increases within 2 weeks in healthy Senegalese men given liquid supplemental zinc, but not zinc-fortified wheat bread. *J Nutr* 2011;141:1369–74.
38. Lo NB, Aaron GJ, Hess SY, *et al*. Plasma zinc concentration responds to short-term zinc supplementation, but not to zinc fortification, in young children in Senegal1,2. *Am J Clin Nutr* 2011;93:1348–55.
39. Wessells KR, Ouedraogo ZP, Rouamba N, *et al*. Short-term zinc supplementation with dispersible tablets or zinc sulfate solution yields similar positive effects on plasma zinc concentration of young children in Burkina Faso: a randomized controlled trial. *J Pediatr* 2012;160:129–35.e3.
40. Soofi S, Cousens S, Iqbal SP, *et al*. Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. *Lancet* 2013;382:29–40.
41. Veenemans J, Schouten LR, Ottenhof MJ, *et al*. Effect of preventive supplementation with zinc and other micronutrients on non-malarial morbidity in Tanzanian pre-school children: a randomized trial. *PLoS ONE* 2012;7:e41630.
42. Gera T, Sachdev HP. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002;325:1142.
43. Zafar SN, Luby SP, Mendoza C. Recall errors in a weekly survey of diarrhoea in Guatemala: determining the optimal length of recall. *Epidemiol Infect* 2010;138:264–9.
44. Feikin DR, Audi A, Olack B, *et al*. Evaluation of the optimal recall period for disease symptoms in home-based morbidity surveillance in rural and urban Kenya. *Int J Epidemiol* 2010;39:450–8.
45. Arnold BF, Galiani S, Ram PK, *et al*. Optimal recall period for caregiver-reported illness in risk factor and intervention studies: a multicountry study. *Am J Epidemiol* 2013;177:361–70.