क्षेत्रीय आयुर्विज्ञान संस्थान, इंफाल: मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
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CIRCULAR

Imphal, the 18th September, 2026

No. 185/RIMS-MRU/2026: It is to notify that, the **16th Research Masterclasses 2026**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, **on 28th September, 2026 (Monday)**.

2. All the faculties (RIMS, Dental College and College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and residents are invited to attend the session at **Banting Hall, RIMS, Imphal**.

Date: 28.09.2026 (Monday)
Time: 3:00 PM onwards
Venue: Banting Hall, RIMS, Imphal **(Designated Site for Participation for RIMS)**
Event Name: Research Masterclass under DHR-ICMR Research Grand Rounds
Speaker Name: Dr. Usha Dhingra, Senior Scientist, Center for Public Health Kinetics, New Delhi.

3. The **research paper** to be discussed during the Masterclass will be uploaded on the **RIMS website** and circulated to the concerned Departments / Colleges through official email.

4. As per the directives issued by the DHR, **maximum participation** from our institute is highly encouraged.

18/09/2026.
(Prof. T. Jeetenkumar Singh)
Nodal Officer
MRU, RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS, Imphal for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH, Imphal for kind information
3. The Dean (Academic), RIMS, Imphal for kind information.
4. The Principal, Dental College, RIMS, Imphal
5. The Principal, College of Nursing, RIMS, Imphal
6. All Heads of Departments, RIMS, RIMS, Imphal
7. The Chairperson/Co-Chairperson, LRAC, MRU, RIMS, Imphal
8. The Internal Member, LRAC, MRU, RIMS, Imphal .....
9. The Member, EC, MRU, RIMS, Imphal .....
10. The Principal Investigator, MRU, RIMS, Imphal .....
11. The IT Cell, RIMS, Imphal – with a request for uploading the notice in the website & technical support on **28.09.26**
12. Asst. Engineer (Elect. /Civil), RIMS, Imphal - with a request for ensuring uninterrupted power supply & optimum AC functioning.
13. The Care Taker, Banting Hall, RIMS, Imphal - for proper upkeep of the venue & accompanying facilities.
14. Guard file.

No. R.11016/03/2025-HR
भारत सरकार/Government of India
स्वास्थ्य एवं परिवार कल्याण मंत्रालय/Ministry of Health & Family Welfare
स्वास्थ्य अनुसंधान विभाग/Department of Health Research

2nd Floor, IRCS Building
Red Cross Road, New Delhi – 110001
Dated14.09.2026

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses for MRU network– reg.

Sir/Madam,

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' proposed around the last Friday of each month. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The next Research Masterclass is scheduled for **28.09.2026 (Monday)** at **3:00 PM**. The speaker is **Dr. Usha Dhingra, Senior Scientist,** Center for Public Health Kinetics, New Delhi. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Your institute is requested to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 25.09.2026. These questions will be discussed with the speaker during masterclass.

Encls: As above

Yours faithfully,

(Dharkat R. Luikang)
Deputy Secretary to the Government of India

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

ORIGINAL ARTICLE

Lower-Dose Zinc for Childhood Diarrhea — A Randomized, Multicenter Trial

Usha Dhingra, M.A., M.C.A., Rodrick Kisenge, M.D., Ph.D., M.Med., Christopher R. Sudfeld, Sc.D., Pratibha Dhingra, Ph.D., Sarah Somji, M.P.H., Arup Dutta, M.B.A., Mohamed Bakari, M.Sc., Saikat Deb, Ph.D., Prabhabati Devi, Ph.D., Enju Liu, M.B., B.S., Ph.D., Aishwarya Chauhan, Ph.D., Jitendra Kumar, Ph.D., Om P. Semwal, M.B., B.S., D.C.H., Said Aboud, M.D., M.Med., Ph.D., Rajiv Bahl, M.B., B.S., M.D., Ph.D., Per Ashorn, M.D., Ph.D., Jonathon Simon, D.Sc., M.P.H, Christopher P. Duggan, M.D., M.P.H., Sunil Sazawal, M.B., B.S., M.P.H., Ph.D., and Karim Manji, M.B., B.S., M.Med., M.P.H.

ABSTRACT

BACKGROUND

The World Health Organization recommends 20 mg of zinc per day for 10 to 14 days for children with acute diarrhea; in previous trials, this dosage decreased diarrhea but increased vomiting.

METHODS

We randomly assigned 4500 children in India and Tanzania who were 6 to 59 months of age and had acute diarrhea to receive 5 mg, 10 mg, or 20 mg of zinc sulfate for 14 days. The three primary outcomes were a diarrhea duration of more than 5 days and the number of stools (assessed in a noninferiority analysis) and the occurrence of vomiting (assessed in a superiority analysis) within 30 minutes after zinc administration.

RESULTS

The percentage of children with diarrhea for more than 5 days was 6.5% in the 20-mg group, 7.7% in the 10-mg group, and 7.2% in the 5-mg group. The difference between the 20-mg and 10-mg groups was 1.2 percentage points (upper boundary of the 98.75% confidence interval [CI], 3.3), and that between the 20-mg and 5-mg groups was 0.7 percentage points (upper boundary of the 98.75% CI, 2.8), both of which were below the noninferiority margin of 4 percentage points. The mean number of diarrheal stools was 10.7 in the 20-mg group, 10.9 in the 10-mg group, and 10.8 in 5-mg group. The difference between the 20-mg and 10-mg groups was 0.3 stools (upper boundary of the 98.75% CI, 1.0), and that between the 20-mg and 5-mg groups was 0.1 stools (upper boundary of the 98.75% CI, 0.8), both of which were below the noninferiority margin (2 stools). Vomiting within 30 minutes after administration occurred in 19.3%, 15.6%, and 13.7% of the patients in the 20-mg, 10-mg, and 5-mg groups, respectively; the risk was significantly lower in the 10-mg group than in the 20-mg group (relative risk, 0.81; 97.5% CI, 0.67 to 0.96) and in the 5-mg group than in the 20-mg group (relative risk, 0.71; 97.5% CI, 0.59 to 0.86). Lower doses were also associated with less vomiting beyond 30 minutes after administration.

CONCLUSIONS

Lower doses of zinc had noninferior efficacy for the treatment of diarrhea in children and were associated with less vomiting than the standard 20-mg dose. (Funded by the Bill and Melinda Gates Foundation; ZTDT ClinicalTrials.gov number, NCT03078842.)

From the Center for Public Health Kinetics, New Delhi, India (U.D., P. Dhingra, A.D., S.D., P. Devi, A.C., J.K., O.P.S., S. Sazawal); Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (R.K., S. Somji, M.B., S.A., K.M.); Harvard T.H. Chan School of Public Health (C.R.S., C.P.D.) and Boston Children's Hospital (E.L., C.P.D.), Boston; and the World Health Organization, Geneva (R.B., P.A., J.S.). Address reprint requests to Dr. Simon at the Department of Maternal, Newborn, Child, Adolescent Health and Ageing, World Health Organization, 20 Ave. Appia, 1211 Geneva 27, Switzerland, or at jonleesimon@gmail.com.

Ms. Dhingra and Dr. Kisenge and Drs. Duggan, Sazawal, and Manji contributed equally to this article.

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Although there has been a 90% decline in diarrhea-related deaths since the 1980s, diarrheal diseases remain a major public health problem. In 2018, approximately 500,000 children died from diarrhea. Most deaths from diarrhea among children could be avoided if children received high-quality case management with the care that has been recommended by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF); this care includes oral rehydration solutions and supplemental zinc.[1,2] The zinc recommendation is based on studies that have shown that administration of supplemental zinc results in a shorter duration of diarrhea, reduces the number of stools and stool output, reduces the risk of persistent diarrhea, and may reduce the risk of subsequent illness and increase weight gain.[3-8]

The recommended zinc dose (20 mg per day for 10 to 14 days) is based on assumptions of increased zinc losses during diarrhea and the need for additional zinc above the recommended dietary allowance for immune and gastrointestinal function.[9] Replication studies have generally used the 20-mg zinc dose without any further dose-ranging analyses. This dose substantially exceeds the recommended dietary allowance of zinc in infancy and early childhood (2 to 5 mg per day).[10]

Zinc given orally can cause vomiting because of its strong metallic taste and tendency to cause gastric irritation.[11] In a meta-analysis of 11 trials involving patients with acute diarrhea (4438 children in total),[4] patients who received supplemental zinc were significantly more likely to vomit after the initial dose of zinc than after the initial dose of placebo (12.7% vs. 7.6%; relative risk, 1.55; 95% confidence interval [CI], 1.30 to 1.84). In another review involving 12 trials (5189 children in total),[12] the risk of vomiting was significantly higher with zinc supplementation than with placebo (risk ratio, 1.59; 95% CI, 1.27 to 1.89).

Lower zinc doses, provided they are equally effective, might have the advantage of causing less vomiting than the current recommended dose. We therefore performed a randomized, double-blind, controlled trial comparing two lower doses of zinc with the recommended dose in low- and middle-income countries. We hypothesized that lower zinc doses (5 mg or 10 mg per day), as compared with the standard zinc dose (20 mg per day), would be noninferior with respect to treatment efficacy but superior with respect to the side-effect profile (i.e., vomiting).

METHODS

DESIGN

We have published the methods used in this trial previously,[13] and the protocol is available with the full text of this article at NEJM.org. The Zinc Therapeutic Dose Trial was an individually randomized, parallel-group, double-blind, controlled trial of three different doses of zinc among children in India and Tanzania who were 6 to 59 months of age.

To detect diarrhea, trial personnel screened children who presented with illness to outpatient health facilities. Patients were enrolled from periurban outpatient health facilities in India and Tanzania. The trial population was selected to reflect the general population of children presenting with diarrhea who receive ambulatory care in a primary health care setting. The patients were children who had had diarrhea (defined as three or more loose or watery stools in the past 24 hours) for less than 72 hours or dysentery (defined as diarrhea with visible blood), who were likely to stay within the study area for at least 2 months after enrollment, and whose caregivers provided written informed consent.

We excluded children who had severe acute malnutrition (weight-for-length or weight-for-height z score of less than −3 or presence of edema), severe dehydration not correctable within 4 to 6 hours, severe pneumonia (presence of fast breathing or chest in-drawing), or any of the following signs: inability to breast-feed or drink, lethargy or unconsciousness, convulsions, inability to eat without vomiting, clinically suspected bacterial sepsis, rapid diagnostic test–confirmed malaria, or other severe illness. Children who had previously been enrolled in the trial, who were currently enrolled in another study or trial, who had used zinc supplements during the 3 days before enrollment, or who had a sibling currently enrolled in the trial were also excluded.

INTERVENTIONS

Children were randomly assigned to receive one of three regimens: 5 mg, 10 mg, or 20 mg of

zinc administered once daily for 14 days. Study staff instructed caregivers to dissolve the dispersible tablet in 5 to 10 ml of water or breast milk immediately before administration. After receiving an initial dose under direct supervision of trial staff on the day of enrollment, children received zinc from their caregivers for 14 days in total. Zinc tablets were purchased from Laboratoires Pharmaceutiques Rodael, who manufactured the tablets and shipped them to the WHO for randomization and labeling before they were shipped to the study sites.

OUTCOMES

The primary efficacy outcomes were diarrhea lasting for more than 5 days and the number of loose or watery stools during the diarrhea episode after randomization. We defined diarrhea as the occurrence of three or more loose or watery stools per day. The primary safety outcome was the occurrence of vomiting within 30 minutes after administration of any zinc dose. This dose-related vomiting was measured by direct observation on day 1 and subsequently by caregiver report recorded in a daily diary. Caregivers also used the daily diary to record the zinc doses given, number of stools, and non–dose-related vomiting (>30 minutes after dose administration). This diary was reviewed by trained field workers at periodic home, clinic, or telephone visits on days 3, 5, 7, 10, and 15.

Secondary outcomes included diarrhea lasting longer than 3 days, the number of tablets consumed, caregiver reporting of favorable acceptability of zinc to the child, illness (diarrhea, fever, or respiratory symptoms) during the 60-day period after treatment initiation, growth (changes in weight, length, and mid–upper arm circumference) during the 60-day period after treatment initiation, and plasma zinc levels on days 1, 3, 7, 15, 21, and 30. To assess zinc levels during the follow-up period, two blood specimens were obtained from each participant: a randomly selected one third of participants at days 1 and 15, one third at days 3 and 21, and the remaining one third at days 7 and 30 after enrollment.

LABORATORY METHODS

Venous blood specimens (3 to 5 ml) were obtained with the use of a trace element–free syringe, transferred to zinc-free heparin tubes, and spun for 15 minutes, and plasma aliquots were stored in trace element–free tubes at −80°C until analysis.[14] Plasma specimens were analyzed for zinc status with the use of atomic absorption spectrometry (AAS 400, Perkin Elmer).

RANDOMIZATION AND BLINDING

Randomization was stratified according to country (India or Tanzania) and age (<24 months or ≥24 months) (four randomization lists). All three zinc tablets were identical in appearance, taste, and smell and were packaged in identical blister packs. Each pack was labeled only with a unique patient identification number according to a computer-generated permuted block randomization list with variable block size generated off site by a statistician who was not otherwise involved in the trial. The randomization code linking the unique identification number with the treatment group was broken after blinded analysis of all primary outcomes.

STANDARD OF CARE AND ETHICS

All enrolled children received standard of care for diarrhea management in accordance with WHO and UNICEF diarrhea case-management guidelines.[15] All caregivers signed written informed consent for their child's participation. The protocol was approved by the WHO Ethics Review Committee, the institutional review board of Boston Children's Hospital, the Tanzania Food and Drug Authority, the Tanzanian National Institute of Medical Research, the Muhimbili University of Health and Allied Sciences, Dar es Salaam, and the institutional ethics committee of Subharti Medical College and Hospital, Meerut, India. The data and safety monitoring board met twice during the trial and did not recommend any changes in the trial conduct. The authors vouch for the accuracy of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

Assuming 1:1:1 random randomization, a 0.05 significance level (one-sided for the noninferiority tests for diarrhea duration and mean stool number and two-sided for the superiority test for vomiting), 90% power, and a 5% loss to follow-up, we calculated that 4500 patients were needed.[13] The assumptions used for sample-size calculation, including noninferiority and superiority

margins, are described in a separate article on methods (included in the Supplementary Appendix, available at NEJM.org).

All primary analyses used the intention-to-treat principle, and sensitivity analyses were performed with the use of a per-protocol approach for noninferiority outcomes.[16] The intention-to-treat analysis included all patients who underwent randomization and for whom assessable data were available, and the per-protocol analysis included patients for whom documentation showed that they had taken zinc for at least the first 5 days after randomization.

Children who did not have resolution of diarrhea, were lost to follow-up, died, or withdrew before day 5 were not included in the analysis of the first efficacy variable. Binomial generalized estimating equations with identity link were used to estimate the risk differences between the lower-dose groups and the standard-dose group.[17,18] The confidence intervals of these risk differences were compared with a prespecified noninferiority margin of 4 percentage points. We also constructed a Kaplan–Meier curve for the time to recovery from diarrhea in each group and used the log-rank test to test the differences.

Analysis of covariance was used to estimate the mean differences in the total number of loose or watery stools between the lower-dose groups and the standard-dose group and their confidence intervals. These confidence intervals were compared with a prespecified noninferiority margin of 2 loose or watery stools.

For the safety outcome of vomiting within 30 minutes after zinc administration, generalized estimating equations with the log link, binomial distribution, exchangeable correlation matrix, and robust estimators of variance were used to assess the relative risk of vomiting with lower doses as compared with standard doses and their confidence intervals.

We performed post hoc Bonferroni correction for the primary efficacy outcomes by providing 98.75% confidence intervals to account for multiple comparisons (duration of diarrhea and number of stools, 10 mg vs. 20 mg and 5 mg vs. 20 mg). Similar correction was applied to the primary safety outcome (vomiting) by providing 97.5% confidence intervals (10 mg vs. 20 mg and 5 mg vs. 20 mg).

We used a linear mixed-effects model to assess differences in plasma zinc response among the three groups. The model included treatment group, the day that the blood specimen was obtained, and an interaction term between these two variables. Relative risks or mean differences with their 95% confidence intervals were calculated for other secondary outcomes. They were not adjusted for multiple comparisons. Although the trial was not designed to draw conclusions about treatment-effect modification, prespecified exploratory subgroup analyses based on baseline characteristics were performed. Stratified risk differences and relative risks and their 95% confidence intervals are shown.

Statistical analyses were performed with Stata software, version 14 (StataCorp), SPSS software, version 25 (SPSS), and SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From January 2017 to February 2019, we screened 5676 children with diarrhea and enrolled 4500 children. One third of the children were randomly assigned to each treatment group (Fig. S1 in the Supplementary Appendix). Follow-up for primary outcomes was complete for approximately 98% of the enrolled children. For the primary outcome of diarrhea duration of more than 5 days, data were available for more than 98% of the patients (1480 of 1504 patients in the 5-mg group, 1480 of 1498 patients in the 10-mg group, and 1479 of 1498 patients in the 20-mg group); for the total number of stools, data were available for more than 99% (1496 of 1504, 1488 of 1498, and 1490 of 1498, respectively). Because the children were directly observed during the 30 minutes after the first dose, data were available for 100% of the patients for the primary outcome of vomiting within 30 minutes. For plasma zinc levels, the percentage of patients with data missing varied according to the day that the blood specimen was obtained and ranged from 13% to 26%.

Baseline characteristics were generally well balanced among the three groups (Table 1). The mean (±SD) ages of the children were 23.0±14.8 months in the 5-mg group, 22.7±14.6 months in the 10-mg group, and 23.2±15.3 months in the 20-mg group. The majority of children had no

Table 1. Baseline Characteristics of the Trial Population.*

Characteristic	5-mg Group (N=1504)	10-mg Group (N=1498)	20-mg Group (N=1498)
Study site — no. (%)			
India	753 (50.1)	749 (50.0)	748 (49.9)
Tanzania	751 (49.9)	749 (50.0)	750 (50.1)
Maternal and household characteristics			
Maternal age — yr†	26.7±5.0	26.8±5.0	26.9±5.0
Maternal education — yr‡	7.3±4.2	7.1±4.1	7.3±4.0
Household wealth above median — no./total no. (%)§	760/1499 (50.7)	738/1496 (49.3)	772/1496 (51.6)
Child characteristics			
Age at randomization — mo	23.0±14.8	22.7 ±14.6	23.2±15.3
Age group at randomization — no. (%)			
6 to <12 mo	412 (27.4)	410 (27.4)	434 (29.0)
12 to <24 mo	499 (33.2)	502 (33.5)	476 (31.8)
24 to <60 mo	593 (39.4)	586 (39.1)	588 (39.3)
Female sex — no. (%)	711 (47.3)	725 (48.4)	719 (48.0)
Breast-feeding on day before enrollment — no./total no. (%)	876/1499 (58.4)	857/1496 (57.3)	853/1495 (57.1)
Rotavirus vaccination — no./total no. (%)¶	749/1503 (49.8)	741/1498 (49.5)	748/1496 (50.0)
Duration of diarrhea before enrollment — no. (%)			
≤24 hr	58 (3.9)	48 (3.2)	59 (3.9)
25 to 48 hr	1259 (83.7)	1224 (81.7)	1231 (82.2)
49 to <72 hr	187 (12.4)	226 (15.1)	208 (13.9)
No. of loose or watery stools in the 24 hr before enrollment	5.7±2.0	5.7±2.1	5.7±2.1
Dysentery — no./total no. (%)	54/1503 (3.6)	62/1497 (4.1)	51/1497 (3.4)
Some dehydration — no. (%)‖	32 (2.1)	11 (0.7)	13 (0.9)
Axillary temperature >38°C — no. (%)	48 (3.2)	40 (2.7)	34 (2.3)
Cough or difficulty breathing — no. (%)	405 (26.9)	438 (29.2)	424 (28.3)
Observed respiratory rate >40 breaths/min — no. (%)	86/1503 (5.7)	84/1497 (5.6)	85/1497 (5.7)
Previous use of antibiotic agent — no. (%)	32/1499 (2.1)	38/1496 (2.5)	26/1496 (1.7)
z Score			
Length or height for age	−1.3±1.2	−1.3±1.1	−1.3±1.2
Weight for length or height	−0.7±1.0	−0.7±1.0	−0.7±1.0
Weight for age	−1.2±1.1	−1.2±1.0	−1.2±1.1
Mid–upper-arm circumference for age	−0.8±1.0	−0.8±1.0	−0.8±1.0
Zinc dose — mg/kg of body weight	0.53±0.13	1.07±0.25	2.14±0.54
Plasma zinc concentration — μg/dl**	71.5±23.4	74.9±23.9	74.0±27.1
Plasma zinc concentration <65 μg/dl — no./total no. (%)**	175/436 (40.1)	143/432 (33.1)	174/441 (39.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for plasma zinc to micromoles per liter, multiply by 0.1530.

† Data were missing for 13 patients in the 5-mg group, 8 patients in the 10-mg group, and 9 patients in the 20-mg group.

‡ Data were missing for 18 patients in the 5-mg group, 11 patients in the 10-mg group, and 16 patients in the 20-mg group.

§ A country-specific household wealth index was constructed by means of a principal components analysis of household ownership, household assets, drinking water source, and sanitation.

¶ More than 99% of Tanzanian children received at least one rotavirus vaccination, whereas less than 1% of children in India received at least one rotavirus vaccination.

‖ The World Health Organization Integrated Management of Childhood Illness (IMCI) definition of dehydration was used, which requires two of the following signs: restlessness and irritability, sunken eyes, thirst, eager drinking, and skin that goes back slowly when pinched.

** Plasma zinc concentrations were assessed in a random sample of 33.3% of patients at baseline at each site.

Table 2. Effect of Zinc Supplementation Dose on Diarrhea and Vomiting in Children with Acute Diarrhea.

Outcome	5-mg Group (N=1504)	10-mg Group (N=1498)	20-mg Group (N=1498)
Diarrhea-related outcomes			
Diarrhea >5 days, intention-to-treat analysis			
No./total no. (%)	106/1480 (7.2)	114/1480 (7.7)	96/1479 (6.5)
Risk difference (upper boundary of one-sided 98.75% CI) — percentage points*	0.7 (2.8)	1.2 (3.3)	Reference
One-sided P value for noninferiority†	<0.001	0.002	Reference
Diarrhea >5 days, per-protocol analysis			
No./total no. (%)	102/1431 (7.1)	109/1437 (7.6)	93/1440 (6.5)
Risk difference (upper boundary of one-sided 98.75% CI) — percentage points	0.7 (2.8)	1.1 (3.3)	Reference
Total loose or watery stools after enrollment, intention-to-treat analysis			
No. of patients with data	1496	1488	1490
Mean no. of stools	10.8±8.9	10.9±9.2	10.7±8.7
Mean difference (upper boundary of one-sided 98.75% CI) — no. of stools*	0.1 (0.8)	0.3 (1.0)	Reference
One-sided P value for noninferiority‡	<0.001	<0.001	
Total loose or watery stools after enrollment, per-protocol analysis			
No. of patients with data	1431	1437	1410
Mean no. of stools	10.8±8.9	11.0±9.3	10.6±8.2
Mean difference (upper boundary of one-sided 98.75% CI) — no. of stools	0.2 (0.9)	0.3 (1.1)	Reference
Vomiting-related outcomes			
Any vomiting over 14-day period within 30 min after dosing			
No./total no. (%)	206/1504 (13.7)	233/1498 (15.6)	289/1498 (19.3)
Relative risk (97.5% CI)§	0.71 (0.59–0.86)	0.81 (0.67–0.96)	Reference
Two-sided P value for superiority§	<0.001	0.01	
Any vomiting over 14-day period more than 30 min after dosing			
No./total no. (%)	301/1496 (20.1)	333/1488 (22.4)	403/1490 (27.0)
Relative risk (95% CI)	0.74 (0.65–0.85)	0.83 (0.73–0.94)	Reference

* A post hoc Bonferroni correction was applied to the primary efficacy outcomes to account for tests of the two efficacy outcomes and two treatment groups; 98.75% confidence intervals are shown, and a P value of less than 0.0125 was considered to indicate statistical significance (0.05 over four tests).
† The margin for noninferiority was 4 percentage points.
‡ The margin for noninferiority was 2 stools.
§ A post hoc Bonferroni correction was applied to the primary safety outcome to account for tests of the two treatment groups; 97.5% confidence intervals are shown, and a P value of less than 0.025 was considered to indicate statistical significance (0.05 over two tests).

dehydration at presentation, and the mean number of loose or watery stools in the 24 hours before enrollment was 5.7 in all three groups. Additional baseline characteristics are shown in Table S1. Baseline characteristics according to trial site are provided in Tables S2 and S3.

PRIMARY OUTCOMES

In the intention-to-treat analysis of the first primary efficacy outcome, the percentage of children who had diarrhea with a duration of more than 5 days was similar in the three groups (7.2% in the 5-mg group, 7.7% in the 10-mg group, and 6.5% in the 20-mg group) (Table 2). The risk in the 10-mg group was 1.2 percentage points higher than that in the 20-mg group (upper boundary of the one-sided 98.75% CI, 3.3), and the risk in the 5-mg group was 0.7 percentage points higher than that in the 20-mg group (upper boundary of the one-sided 98.75% CI,

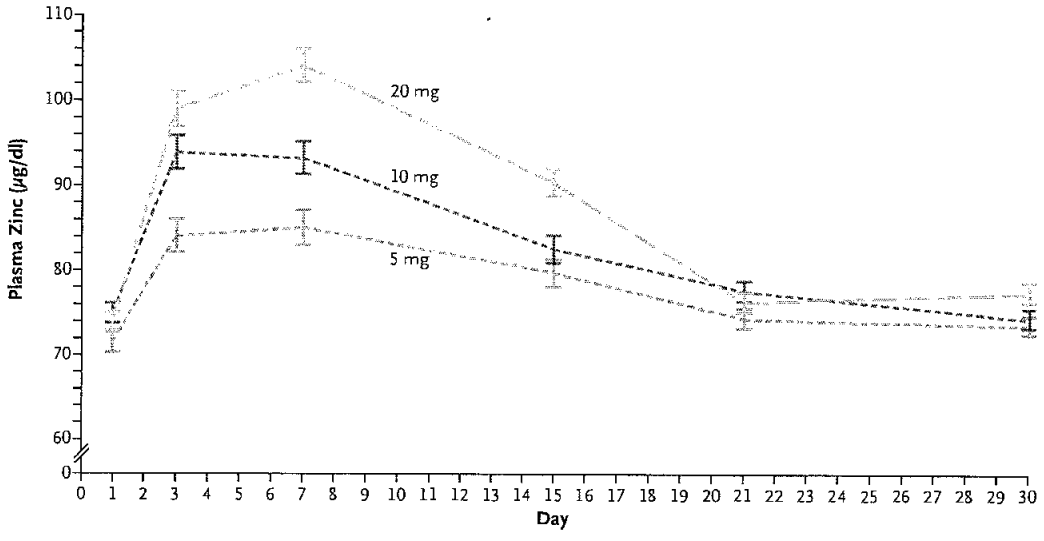

Figure 1. Modeled Plasma Zinc Concentrations.

Linear mixed-effects model estimates of the mean plasma zinc concentrations are shown; I bars indicate the SE. Plasma zinc testing was planned for 1500 patients at each of the pair of time points: day 1 (baseline) and day 15, days 3 and 21, and days 7 and 30. Plasma zinc concentrations were missing for 191 of 1500 patients (13%) on day 1, for 333 of 1500 (22%) on day 3, for 270 of 1500 (18%) on day 7, for 384 of 1500 (26%) on day 15, for 343 of 1500 (23%) on day 21, and for 247 of 1500 (16%) on day 30.

2.8). In both cases, the upper boundary of the confidence interval was lower than the prespecified 4-percentage-point noninferiority margin. Results from the per-protocol analyses were similar. Kaplan–Meier curves for the time to recovery from diarrhea are shown in Figure S4.

The intention-to-treat analysis of the second efficacy outcome showed that the mean number of loose or watery stools was similar in the three groups: 10.8±8.9 in the 5-mg group, 10.9±9.2 in the 10-mg group, and 10.7±8.7 in the 20-mg group (Table 2). The children assigned to the 10-mg group had a mean of 0.3 more loose stools (upper boundary of the one-sided 98.75% CI, 1.0) and children assigned to the 5-mg group had a mean of 0.1 more loose stools (upper boundary of the one-sided 98.75% CI, 0.8) than children in the 20-mg group. In both cases, the upper boundary of the 98.75% confidence interval was lower than the prespecified noninferiority margin of 2 stools. Results from per-protocol analyses were similar.

The effect of lower zinc doses on the risk of vomiting is shown in Table 2. Children in the 5-mg group had a 29% lower risk of vomiting within 30 minutes after zinc administration than children in the 20-mg group (relative risk, 0.71; 97.5% CI, 0.59 to 0.86). Children in the 10-mg group had a 19% lower risk of vomiting within 30 minutes after zinc administration than children in the 20-mg group (relative risk, 0.81; 97.5% CI, 0.67 to 0.96). Similar effects were seen for vomiting beyond 30 minutes after zinc administration (Table 2).

Results of subgroup analyses of the primary outcomes are shown in Tables S4, S5, and S6. The lower doses of zinc appeared to have larger beneficial effects on vomiting among patients in India than among those in Tanzania. Use of rotavirus vaccine also appeared to modify the effect size for vomiting, but this exposure was confounded with study site. The results of other subgroup analyses were unremarkable.

SECONDARY OUTCOMES

Figure 1 shows the mean and standard error of plasma zinc concentrations on day 1 (baseline), day 3, day 8, day 15, day 21, and day 30 in each treatment group. Plasma zinc concentrations were similar in the three groups at baseline but were lower in the 5-mg and 10-mg groups than in the 20-mg group on days 3, 7, and 14 after dosing. These differences were no longer seen on day 21 and day 30 (Table S7).

Results for secondary outcomes are shown in Table 3. The three groups had similar percentages of children with diarrhea, fever, or fast or difficult breathing at 30, 45, and 60 days of follow-up. Growth during the 60-day follow-up period and anthropometric status at the end of the follow-up period were also similar in the three groups, with the exception of the 5-mg group having a higher percentage of children with stunting than the 20-mg group at the end of follow-up. However, the observed differences in stunting between each lower-dose group and the 20-mg group were similar at baseline.

Adherence to the intervention was very high and similar in the three groups. Of the expected 14 pills, a mean of 13.5±2.1 pills was consumed by children in the 5-mg group, 13.7±1.7 by children in the 10-mg group, and 13.6±1.8 by children in the 20-mg group. More than 80% of the caregivers in each of the three groups (82.9% in the 5-mg group, 80.8% in the 10-mg group, and 81.1 in the 20-mg group) reported favorable acceptance of the treatment by their children.

DISCUSSION

In this large, multicenter clinical trial, lower doses of zinc (5 mg or 10 mg daily for 14 days) were noninferior to the standard dose of zinc (20 mg) in terms of duration of diarrhea and mean number of stools in children with acute diarrhea. Both the 5-mg and the 10-mg doses were superior to the 20-mg dose with respect to vomiting.

Vomiting is often a part of the acute diarrhea syndrome. Meta-analyses have shown a 50% higher risk of vomiting among children taking zinc supplements.[4,12] Efforts to scale up the use of zinc have highlighted the elevated risk of vomiting as a consideration in the rollout of such programs.[19] Reduced vomiting may improve food intake and alleviate parents' concerns about the severity of illness. In our trial, adherence to therapy was very high and did not differ significantly among the groups, despite the lower risk of vomiting associated with lower zinc doses. However, our study was an efficacy trial in which substantial efforts were made to achieve high adherence. Thus, our findings with respect to adherence might not be generalizable to program conditions.

We also found a potential effect modification according to site, in that children in India appeared to benefit more from lower zinc doses with respect to vomiting than did children in Tanzania. In addition to differing with respect to their country of origin and possibly other, unmeasured factors, the cohorts of children from the two countries included in the trial differed with respect to age (Tanzanian children were younger), nutritional status (Indian children were less well nourished), and rotavirus vaccine coverage (high in Tanzania and very low in India). Although we did not collect data on the underlying causes of diarrhea, it is possible that Indian children, because of the lack of a nationwide rotavirus immunization program, were more likely to have rotavirus as a cause of their symptoms.[20] In places where the rotavirus vaccine has been implemented, norovirus and sapovirus are common causes of childhood diarrhea.[21] Data on the potential differential effect of supplemental zinc according to the cause of diarrhea are limited.[22] Stratified analyses also suggested the possibility that children with stunting, who may be at higher risk for adverse effects of diarrheal diseases,[1,23] had greater benefit with respect to the risk of vomiting with the lower doses as compared with the 20-mg regimen.

The physiological basis for the effects of zinc supplementation on diarrheal diseases is not completely clear.[24] Possible mechanisms include correction of a nutrient deficiency, improvement of immune function,[25] or inhibition of cyclic AMP–mediated chloride secretion.[26] The doses we studied in the trial (5 mg and 10 mg daily) still exceed the recommended daily allowance for young children, and therefore it is plausible that they still work through these suggested mechanisms of action.

Strengths of our trial include its randomized, double-blind, multicenter design, large sample size, high rates of follow-up, location in countries in south Asia and sub-Saharan Africa, and recruitment of patients in outpatient facilities, where the majority of diarrhea is managed globally. Our trial addresses an important knowledge gap presented by the empirical use of the 20-mg zinc dose, which was recommended for global use without rigorous dose-finding trials.

Limitations of our trial include the reliance on caregiver reports for outcomes (although these were verified with frequent patient contact

Table 3. **Effect of Zinc Supplementation Dose on Selected Secondary Outcomes.**

Outcome	5-mg Group (N=1504)	Relative Risk or Mean Difference, 5 mg vs. 20 mg (95% CI)*	10-mg Group (N=1498)	Relative Risk or Mean Difference, 10 mg vs. 20 mg (95% CI)*	20-mg Group (N=1498)
Serious adverse event within 60 days — no. (%)	12 (0.8)	1.33 (0.56 to 3.14)	7 (0.5)	0.78 (0.29 to 2.08)	9 (0.6)
Diarrhea continuing beyond 3 days — no./total no. (%)†	333/1481 (22.5)	1.03 (0.90 to 1.18)	333/1481 (22.5)	1.03 (0.90 to 1.18)	323/1480 (21.8)
No. of tablets consumed during 14-day treatment period	13.53±2.05	−0.05 (−0.19 to 0.09)	13.65±1.71	0.06 (−0.06 to 0.19)	13.58±1.83
Diarrhea in the 14-day period before day 30 — no./total no. (%)	104/1433 (7.3)	0.90 (0.70 to 1.16)	104/1449 (7.2)	0.89 (0.69 to 1.15)	116/1437 (8.1)
Fever in the 14-day period before day 30 — no./total no. (%)	149/1433 (10.4)	1.12 (0.90 to 1.40)	139/1449 (9.6)	1.04 (0.83 to 1.30)	133/1437 (9.3)
Fast or difficult breathing in the 14-day period before day 30 — no./total no. (%)	8/1432 (0.6)	1.34 (0.47 to 3.84)	10/1449 (0.7)	1.65 (0.60 to 4.53)	6/1436 (0.4)
Ease in supplement administration reported by caregiver — no./total no. (%)	1187/1447 (82.0)	1.01 (0.97 to 1.04)	1174/1453 (80.8)	0.99 (0.96 to 1.03)	1182/1452 (81.4)
Anthropometric measures at day 60					
Change in z score for length or height-for age‡	−0.11±0.34	−0.01 (−0.04 to 0.01)	−0.10±0.34	−0.005 (−0.03 to 0.02)	−0.10±0.33
Change in z score for weight for age§	0.10±0.35	0.02 (−0.007 to 0.05)	0.10±0.35	0.02 (−0.004 to 0.05)	0.08±0.35
Change in z score for weight for length or height¶	0.19±0.54	0.03 (−0.01 to 0.07)	0.18±0.55	0.03 (−0.01 to 0.07)	0.16±0.54
Change in z score for mid–upper arm circumference for age‖	0.21±0.40	0.02 (−0.008 to 0.05)	0.21±0.40	0.03 (−0.005 to 0.06)	0.18±0.41
Stunting — no./total no. (%)**	405/1354 (29.9)	1.16 (1.03 to 1.31)	386/1356 (28.5)	1.11 (0.98 to 1.25)	350/1357 (25.8)
Wasting — no./total no. (%)††	86/1354 (6.4)	0.85 (0.64 to 1.12)	102/1350 (7.6)	1.01 (0.77 to 1.31)	102/1360 (7.5)
Underweight — no./total no. (%)‡‡	284/1367 (20.8)	1.08 (0.93 to 1.26)	273/1370 (19.9)	1.04 (0.89 to 1.21)	262/1363 (19.2)
Favorable child acceptability reported by caregiver — no./total no. (%)	1199/1447 (82.9)	1.02 (0.99 to 1.06)	1174/1453 (80.8)	1.00 (0.96 to 1.03)	1177/1452 (81.1)
Reduction in diarrhea severity reported by caregiver — no./total no. (%)	1300/1446 (89.9)	1.00 (0.97 to 1.02)	1315/1453 (90.5)	1.00 (0.98 to 1.03)	1309/1453 (90.1)

* For outcomes analyzed as numbers and percentages of patients, the relative risk and 95% confidence interval are reported. For outcomes analyzed as means and SD, the difference in the mean and the 95% confidence interval are reported.
† Total numbers are the number of children at risk.
‡ Data were available for 1355 patients in the 5-mg group, for 1357 in the 10-mg group, and for 1357 in the 20-mg group.
§ Data were available for 1367 patients in the 5-mg group, for 1370 in the 10-mg group, and for 1363 in the 20-mg group.
¶ Data were available for 1354 patients in the 5-mg group, for 1350 in the 10-mg group, and for 1360 in the 20-mg group.
‖ Data were available for 1333 patients in the 5-mg group, for 1330 in the 10-mg group, and for 1346 in the 20-mg group.
** Stunting was defined as a z score for length or height for age of less than −2 SD.
†† Wasting was defined as a z score for weight for length or height of less than −2 SD.
‡‡ Underweight was defined as a z score for weight for age of less than −2 SD.

and daily recording of outcome information in the diary card). In addition, the modest rate of participation of children with severe diarrheal disease is likely to have contributed to lower-than-anticipated frequency of episodes lasting longer than 5 days. Our patients, however, are representative of those who present with diarrhea to first-level health facilities in low- and middle-income countries and are given oral rehydration solution and zinc treatment.

Despite evidence supporting the efficacy of supplemental zinc in improving outcomes in patients with diarrhea, as well as strong recommendations from policymakers, programmatic uptake of this component of diarrhea management has been slow to achieve high levels of coverage.[1,27] Evaluations of this limited coverage highlight the supply-side problems of insufficient financial and human capital and a weak global supply chain.[28] A renewed public health push will be needed to solve these problems and maximize the benefits of this intervention. Our findings may contribute to these programmatic efforts.

In our trial, we found that children with acute diarrhea receiving 5 mg or 10 mg per day of supplemental zinc had diarrhea outcomes similar to those in children receiving 20 mg but had less vomiting.

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No potential conflict of interest relevant to this article was reported.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Appendix

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All four co-Principal Investigators (SSa, UD, KM, CD) along with WHO staff (JS, PA, RB) conceptualized the project, designed the study and provided overall scientific leadership. Site Coordinators (PD and SSo) oversaw the field operations. Data Analysis was led by CS, EL, MB, AD, and UD and interpretation was done in close consultation with the co-PIs and WHO staff. Laboratory analysis was coordinated by SD. CD wrote the first draft of the manuscript. All authors

critically reviewed and revised the draft and contributed to the intellectual contents of the manuscript. All authors approved the final version of the manuscript.

Methods Paper

Effect of dose reduction of supplemental zinc for childhood diarrhoea: study protocol for a doublemasked, randomised controlled trial in India and Tanzania

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Abstract

Background Diarrhoea-associated mortality and morbidity are highest in infants and young children in low-income and middle-income countries (LMICs). Zinc supplementation during acute diarrhoea has been shown to reduce the duration of illness and the risk of persistent diarrhoea. However, vomiting with zinc supplementation is a common side effect that may interfere with compliance and programmatic scale-up, and may be related to the dose prescribed.

Methods/design The Zinc Therapeutic Dose Trial
(ZTDT) is a two-centre (Tanzania and India), three-arm randomised, double-blind controlled non-inferiority trial.
Children 6–59 months of age with acute diarrhoea are eligible to participate. Enrolled children (1500 per arm; 4500 total) will be randomly allocated to receive 5, 10 or 20 mg of zinc sulfate daily for 14 days and will be followed up for 60 days after enrolment. All children will receive WHO/Unicef Integrated Management of Childhood Illness standard of care (oral or intravenous rehydration and zinc as indicated and feeding advice). The primary efficacy outcomes of the trial are the percentage of subjects with diarrhoea duration >5days, the mean total number of loose or watery stools after enrolment and the proportion of children vomiting within 30 min of zinc administration.

Discussion The ZTDT trial will determine the optimal dose of therapeutic zinc supplements for treatment of acute diarrhoea in children aged 6–59 months in two LMICs. The results of the trial are likely to be generalisable to childhood acute diarrhoea in similar resource-limited settings and may influence global policy about zinc supplementation dosage during acute diarrhoea.

Trial registration number NCT03078842.

Trial status Enrolment began in January 2017 and follow-up is estimated to be completed by April 2019. As of 1 February 2019, 742 children are still contributing data to the ZTDT study.

What is already known on this topic?

- Therapeutic zinc supplementation has been recommended by WHO/Unicef for standard diarrhoea case management since 2004.
- Research evidence had shown zinc reduced the duration and severity of the acute diarrhoea, and lowered the risk of persistent diarrhoea.
- However, many trials noted that current dosage (20 mg/day for children aged >6 months) is associated with vomiting and possibly poor compliance.

What this study hopes to add?

- This study evaluates whether lower doses of zinc (10 mg/5 mg) are non-inferior to the standard dose in efficacy but superior for vomiting.
- If vomiting is less frequent and efficacy is maintained with low-dose zinc, caregiver acceptability may improve, leading to greater utilisation and better health outcomes.

Background

Zinc is a vital micronutrient essential for protein synthesis, cell growth and differentiation, immune function, and intestinal transport of water and electrolytes.1 Zinc is also important for normal growth and development of children both with and without diarrhoea.2 Zinc deficiency is associated with an increased risk of gastrointestinal infections, altered structure and function of the gastrointestinal tract and impaired immune function. 3–5 Dietary deficiency of zinc is especially common in low-income countries because of a low dietary intake of zinc-rich foods (including foods of animal origin) or low bioavailability due to the presence of phytates often found in cereal-
based diets.1

The benefits of zinc supplementation in the management of diarrhoea have been observed in several studies. Patel *et al*6 noted in a systematic review and meta-analysis an approximate 20% reduction in the mean duration of acute diarrhoea with zinc supplementation. Lazzerini and Wanzira,7

summarising data from 2581 children from 9 trials, noted that children older than 6 months receiving zinc supplements had a shorter diarrhoea duration by about half a day (mean difference −11.46 hours, 95% CI −19.72 to −3.19). A reduction in diarrhoea that continues up to day 7 (risk ratio 0.73, 95% CI 0.61 and 0.88) was also noted in this study. Moreover, the study indicated that zinc supplements in children with persistent diarrhoea (defined as diarrhoea for >14 days) also may shorten average diarrhoea duration by 16 hours (mean difference −15.84 hours, 95% CI −25.43 to −6.24). As a result of these and other trials, since 2005 WHO/Unicef have recommended routine zinc supplementation (10 mg daily for infants below 6 months of age; 20 mg daily for children older than 6 months) for 10–14 days.8

These doses, however, were not chosen after dose ranging studies, and substantially exceed the recommended dietary allowances (RDA) for zinc in infancy and early childhood (2–5 mg/day).9 High doses of zinc can cause epigastric pain and lethargy, and its metallic taste can also induce vomiting. Vomiting with zinc supplements is a common side effect noted in many published trials. A meta-analysis by Lukacik *et al* 3 summarised the findings for acute and persistent diarrhoea from a total of 22 zinc intervention trials, using a range of zinc dosing (5–45 mg/day). In 11 acute diarrhoea trials (n=4438),
the proportion of participants who vomited after the initial dose was significantly higher with zinc use than with placebo (12.7% vs 7.6%; relative risk [RR]: 1.55; 95% CI: 1.30 to 1.84; p≤0.001). According to the review by Lazzerini and Wanzira,7 the risk of vomiting increased with zinc supplementation in both children older than age 6 months (risk ratio 1.57, 95% CI 1.32 to 1.86; 2605 children, 6 trials) as well as children younger than 6 months of age (risk ratio 1.54, 95% CI 1.05 to 2.24; 1334 children, 2 trials).
Other studies have also reported that therapeutic zinc supplementation during diarrhoea causes higher rates of vomiting.10–12

Thus, although substantial evidence supports the efficacy of zinc supplementation during episodes of diarrhoea, vomiting is significantly more common among supplemented children. Lower doses of zinc, provided they are equally effective, might have the advantage of reducing side effects, increasing compliance and programmatic roll-out. If the zinc dose for diarrhoea treatment and zinc deficiency can be uniform, then the national essential drug lists can be simplified. Therefore, there exists an important rationale to identify the dose of zinc supplementation associated with both efficacy and an improved safety profile. We present the protocol for a two-centre, randomised, double-blind controlled trial of
three doses of zinc conducted in Tanzania and India. The overall goals of the study are to evaluate the non-inferiority, safety and acceptability of the two lower zinc doses (5 and 10 mg/day) versus standard zinc dose (20 mg/day).

Methods

Study design

The Zinc Therapeutic Dose Trial (ZTDT) is an individually randomised, parallel-group, double-blind, controlled trial of three doses of supplemental zinc conducted among 4500 children aged 6–59 months in India and Tanzania (ClinicalTrials. gov identifier NCT03078842).

The trial protocol was developed by collaborators at WHO, Department of Maternal Newborn, Child and Adolescent Health (Geneva, Switzerland) together with teams in New Delhi, India (Centre for

Public Health Kinetics), Dar es Salaam, Tanzania (Muhimbili University of Health and Allied Sciences) and Boston, USA (Boston Children's Hospital and Harvard TH Chan School of Public Health). The ZTDT protocol diagram is presented in online supplementary additional file 1. The schedule of trial enrolment, interventions and assessments is presented in online supplementary additional file 2. The first participant was enrolled in the trial in January 2017 in India and March 2017 in Tanzania and follow-up data collection will continue through approximately April 2019. This paper follows the Standard Protocol Items: Recommendations for Interventional trials (SPIRIT) checklist (see online supplementary additional file 3).

The study population will include 4500 children aged 6–59 months with diarrhoea of <72 hours duration. Enrolled children will be followed up for 60 days after randomisation. The participant will be followed up closely for the first 15 days to record postintervention morbidity outcomes and to ensure compliance with study regimen. Study participants will be assessed again at 30, 45 and 60 days post-enrolment to estimate impact on long-term morbidity outcomes.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Primary and secondary objectives

he overall aim of ZTDT is to identify the optimal dose of zinc in children under 5 years with acute diarrhoea.

The primary aims of the study are: (1) to assess whether lower doses of zinc (5 or 10 mg/day) are at least as effective as the standard dose of zinc (20 mg/day) in children aged 6–59 months, in terms of burden of illness (percentage of subjects with diarrhoea lasting >5 days; mean number of loose or watery stools during follow-up) and (2) to evaluate the improved effectiveness by reduction in the risk of vomiting in 30 min after receipt of the supplement in low-dose supplemental zinc (5 or 10 mg/day) in comparison to standard dose of zinc (20 mg/day).

Secondary aims of the study are: (1) to explore whether lower doses of zinc have any impact on post-acute illness morbidity outcomes assessed at 30, 45 and 60 days, (2) to explore whether duration of treatment, estimated by mother's reports and collection of used zinc blister packs, has any impact on the primary outcomes, (3) to determine the acceptability of low-dose supplemental zinc compared with standard zinc dose based on an acceptability scale and (4) to determine whether the different doses of zinc are associated with differential plasma zinc levels at days 3, 7, 15, 21 and 30 after randomisation.

Participants/interventions and outcomes

Study setting

The study recruitment sites are in South East Asia (SEA) and sub-Saharan Africa (SSA). In SEA, the study recruitment sites are located in Sangam Vihar, a resettlement colony on outskirts of South Delhi and Harsh Vihar, a semi-urban locality in North East District, Delhi, India. In SSA, recruitment sites are at health centres in Temeke District Hospital, Mbagala Round Table and

Mbagala Rangi Tatu, Dar es Salaam, Tanzania. Both the sites will be recruiting from outpatient health facilities.

Eligibility

Study participants will be eligible for enrolment in the study if they meet the following inclusion criteria: 1) male and female children between 6 and 59 completed months of age, 2) acute diarrhoea duration of <72 hours at the time of screening (defined as three or more loose or watery stools) or dysentery (defined as visible blood in the stool), 3) likely to stay within the study area for the next 2 months and 4) written informed consent is obtained from caretaker.

Children will be excluded if they: (1) have severe acute malnutrition (weight for length/height z-score of <−3 or oedema), (2) have severe dehydration that cannot be corrected within 4–6 hours, (3) have signs of severe pneumonia (characterised by presence of either chest in-drawing and either of the following: convulsions or unconscious or vomiting everything,13 sepsis, rapid diagnostic test (RDT)-confirmed malaria or other severe illness, (4) have previously or currently been enrolled in the study, (5) are currently enrolled in another trial, (6) are not intending to remain in study area for the duration of the study, (7) have a caregiver who declines participation in the study, (8) have other child currently
enrolled in the study in the same household and (9) have used zinc supplements during the 3 days preceding study enrolment.

Sample size

We will enrol 4500 children (1500 per study arm) in the trial. Table 1 presents sample size assumptions and calculations for each of the three primary outcomes. The total sample size for the trial was selected to have at least 90% power for each of the primary outcomes. The primary outcomes (mean number of loose or watery stools post-randomisation and percentage of children with diarrhoea for >5 days) are both based on the non-inferiority hypotheses, while the primary outcome of vomiting post-dose assumes a superiority hypothesis. We assumed 1:1:1 randomisation between the three treatment arms,
a nominal type I error rate (α) of 0.05% and 5% loss to follow-up rate.

Table 1 Sample size calculations for the primary trial outcomes

Outcome	Value in standard dose (20 mg/day) group	Expected value in low-dose groups	Non-inferiority margin	Power, significance level	Sample size per arm (with ~5% attrition)
Duration of diarrhoea, mean (SD)	3.0 (2.7) days	3.0 (2.7) days Lower dose equally effective	0.3 days	90%, 5%	1460
Percentage of children with diarrhoea >5 days	16%	16% Lower dose equally effective	±4%	90%, 5%	1500
Total number of loose or watery stools during follow-up, mean (SD)	10 (9) stools	10 (9) stools Lower dose equally effective	±2 stools	90%, 5%	1460
Percentage of children with vomiting during follow-up	20%	15% Lower dose safer	Not applicable because of superiority hypothesis for this outcome	90%, 5%	1340

Interventions

Children are randomised to receive one of the three zinc sulfate regimens (each taken once daily for 14 days): (1) 5 mg; (2) 10 mg or (3) 20 mg. The zinc tablet (all three regimens) ingredients include aerosil,
maize starch, ethylvanillin (a vanilla flavour), aspartame, magnesium stearate vegetal and vivapur. The three study tablets have identical appearance, taste and smell. The supplement is a dispersible tablet that dissolves in water or breast milk in about 20 s. The caretakers are instructed to dissolve the tablet in 5–10 mL of water or breast milk immediately before administration. Children receive zinc supplementation for 14 days. The first dose of study drug is given at the health facility in which the child is enrolled.

All three doses of the regimen are packaged identically; 10 tablets in 1 blister, 2 blisters in 1 pack (extra doses are provided for redosing in case of vomiting). Each pack is prelabelled with participant ID. Study regimen is manufactured by Laboratoires Pharmaceutiques Rodael, France and shipped to WHO for randomization and labelling, before shipment to recruitment sites (as described in 'Randomisation, allocation, concealment and masking' section).

Adherence assessment
Adherence to the study regimen is optimised by close follow-up: either in person (clinic/home visits) or telephone contact on days 3, 5, 7, 10 and 15. Adherence to the regimen is measured by counting the numbers of unused tablets during each follow-up visit. Study workers/ research assistants physically count the tablets during home or clinic visits. We give the mother/caregiver a small booklet to record every successful administration as well as any failed attempts to administer the intervention. Study worker reviews the diary card on each visit and collects filled diary card on day 15 visit.

Standard of care
All enrolled children receive standard of care for diarrhoea management per WHO/Unicef, Tanzanian and Indian Ministry of Health guidelines. This includes standardised assessment of hydration status, rehydration and maintenance fluids with intravenous or oral rehydration solutions (ORS) as indicated, recommendation for increased fluid intake and continued feeding at home and instructions on when to seek follow-up care. Children with known HIV receive care and treatment appropriate for the child and referral to the care and treatment centre nearest to the child's home.

Randomisation, allocation, concealment and masking
Trial arm allocation was performed according to a computer-generated randomisation list (generated off-site by a non-study statistician) of 4500 individuals, stratified by country and child age (>6 to <24 months vs >24 to <60 months). A statistician will hold the randomization list codes until completion of primary analyses or until requested by the Data and Safety Monitoring Board (DSMB). Within each stratum, subjects are randomly assigned equally in permuted blocks of variable size to receive one of the three doses of zinc. The purpose of the stratification is to have equal distribution of younger and older children among all three treatment groups. An independent pharmacy team prepared the zinc regimen in Geneva by labelling blister packs with participant IDs based on the randomisation list. Labels were printed at WHO, Geneva and enrolled children were assigned sequential serial numbers. These prelabelled regimens were shipped to the sites in Tanzania and India. The packing and physical appearance of the three study regimes are identical. In addition, the three doses of the regimen are similar in taste, appearance and smell. As a result, the research teams, study staff as well as caregivers

are fully blinded to treatment arm. Zinc formulations are serially numbered according to the randomisation codes. The code is kept in a password-protected spreadsheet file by WHO personnel and is not available to the investigators until the end of the study. This randomisation list was converted into unique sequential serial numbers for each enrolled child at each site. This code will only be broken
if the DSMB requests this information for a participant (should they suspect a relationship of a suspected severe adverse event [SAE] to the study drug) or for a study arm (in their interim analyses).

Data collection, management and analysis

Screening and randomisation
Both sites will be recruiting from community clinics. Surveillance systems are set up at clinics to identify all children presenting with diarrhoea. Trained study staff stationed at each health facility are responsible for identification of children who are potentially eligible. The study team is trained in good clinical practice as well as confidentiality and research ethics.
Written informed consent is sought from the caretaker of children meeting the eligibility criteria. A child can only be enrolled once into the study. The informed consent process includes telling the caretaker that they are free to withdraw from the study at any time, and that participation is entirely voluntary.

Following consent, each participant will be assigned a unique subject identification number. A card detailing the subject ID and the health personnel responsible for enrolment will be provided to the caregiver of enrolled children. The patient locator form/subject master log will be the only link between the subject ID and the participant's name. This information will be stored together with the consent in a locked file cabinet and an online database accessible to only the Project Manager and required study staff for the purpose of patient tracking.

A baseline assessment, including a detailed physical examination (record of vital signs, axillary temperature, respiratory rate, pulse rate, hydration and nutritional status), will be performed by a research physician at the time of screening for enrolment. The child is evaluated for any Integrated Management of Childhood Illness general danger signs (unable/able to drink or breast feed, convulsions,
vomiting, unconscious, stiff neck) and evidence of dehydration or pneumonia, as well as information on
recent medical history (duration of diarrhoea, bloody stool/dysentery, recent fever). Vital signs temperature/heart rate/respiratory rate) in dehydrated child are recorded after the child is rehydrated and stabilised and remaining clinical assessment/screening is completed thereafter. Anthropometry measurements will be taken after rehydration and stabilisation as required, before completing the screening for enrolling the participant. Weight will be measured using an electronic scale with a sensitivity of ±10 g by two independent observers: length (for children aged <24 months) or height (for children aged 24 months or older), which will be measured using a length board within 0.1 cm. Mid-upper arm circumference (MUAC) will be measured using non-stretchable tape to the nearest 0.1 cm. All anthropometric measures will be recorded in duplicate (India) and triplicate (Tanzania). Once these measurements and other eligibility criteria are met, the subject will get enrolled.

Baseline sociodemographic information and vaccination history

Parents of enrolled subjects will be interviewed at study clinic or at home for the baseline sociodemographic characteristics viz. parent's literacy level and occupation, type of house, possession of assets and possible exposures (recent antibiotic use, travel history, water use and filtration and sanitation), breast feeding and vaccination history and information is recorded in the case record forms.

Follow-up visits
Scheduled follow-up visits begin from the third day of the enrolment and are generated daily via an automated visit generation module of the data management software. All children enrolled at the study clinic are to be followed up in the clinic or at home by a trained field worker on day 3, 5, 7, 10, 15, 30, 45 and 60 (online supplementary additional files 1 and 2). In India, study staff will visit the household of enrolled children for all follow-up visitations. If the child is not available at home, a phone call will be made to follow-up the child. In Tanzania, a participant will be followed up at home or clinic on days
3, 7, 15, 30 and 60 and by phone on days 5, 10 and 45. Children still having diarrhoea after day 15 are treated according to standard management guidelines.8 At each visitation during active follow-up period, a study worker asks the mother or other caregiver about the following and records the responses in a predesigned form/data entry module:

1. Ongoing symptoms of diarrhoeal illness, including the number and consistency of stools.
2. Vomiting episodes including any episode within 30 min following zinc administration.
3. Adherence with zinc study regimen ascertained via mothers' recall and/or reported use of zinc tablets
by the child in the Diarrhoea Diary Card and crosschecked by determining the number of unused tablets.
4. Any adverse events, including hospital admissions and deaths of study participants.
5. Criteria for returning to clinic (eg, lethargy, poor oral intake, dehydration).
6. Any other intercurrent illness.
7. Reported use of antibiotics and intravenous/other fluids.

At days 30, 45 and 60 post-enrolment, the study participants are assessed either at the study clinic, via telephone or with a home visit for presence of any illness, diarrhoea, fever, cough or fast or difficult breathing within last 24 hours and any time in past 2 weeks. On the day 60 study completion clinic visit, in addition to morbidity assessment, anthropometric measurements will be taken for each participant using the same procedure as mentioned in the baseline assessment.

Children not available on the visitation day will be visited the next day; if they are still not available, they
are followed-up until found or deemed lost to follow-up. Caregivers are asked to contact the study physicians if they feel that their children are sick between the visits. Children sick on the day of visitation will be referred to the study clinic for a detailed morbidity assessment as well as treatment by the study physician. During each visit, a record of all the medicines and intravenous fluids given, information on number and consistency of stools and data on adherence is recorded in the predesigned forms. Close monitoring will be accomplished through repeated follow-ups during the 14-day regimen period. Every
effort will be made to track and successfully follow-up all randomised children.

Study withdrawal or discontinuation
The participants have the right to withdraw from the study at any time. The subjects will be considered withdrawn from the trial in case of death or lost to follow-up. However, every effort will be made to track and successfully follow-up all enrolled children. The information on withdrawn or discontinued participants will be recorded through a withdrawal slip by field worker and clinic supervisor.

Blood sampling and laboratory investigations
To allow the measurement of the potential differential impact of the varying zinc doses on plasma zinc levels during the follow-up period, each study participant will provide two blood samples. One-third of the study participants will have blood draws at days 1 and 15, one-third at days 3 and 21 and the remaining one-third on days 7 and 30 post-enrolment for assessment of plasma zinc levels.

Blood drawing will follow the protocols of the International Zinc Nutrition Consultative Group (IZINCG).
These include use of powder-free gloves, zinc-free syringes and butterfly, needles and trace element-free blood tubes.14 Plasma is separated at 15 min after blood collection and aliquots are transferred into trace element-free Eppendorf plastic tubes for temporary storage at −20°C and then shipped to central lab for final storage at −80°C in India. In Tanzania, plasma samples are stored in site refrigerators at 2°C–8°C and then shipped to central laboratory storage at −80°C by the end of the day. Plasma zinc concentrations will be measured by atomic absorption spectroscopy (AAS-400 PerkinElmer, USA).

Quality assurance
The persons with at least a secondary school degree will be recruited for data collection team. The following quality assurance checks will be done regularly to ensure highest level of data integrity and quality:
►► An extensive 1–3 weeks training session for data collectors to ensure the interdata collector reliability is above 95%.
►► Pilot field data testing is monitored closely by the research scientist(s) responsible for quality assurance.
►► Real-time electronic data capture will ensure data validation such as range, logical checks and data
integrity.
►► Interim aggregate data analysis will be carried out periodically for data pattern, heaping, missing values, etc. Based on the feedback, effective measures will be taken to eliminate/minimise the errors.

For overall visit supervision, quality control (QC) supervisors will perform quality checks by visiting at least 10% of the households, re-interviewing 5% respondents and cross-checking these data with concerned field worker. QC supervisors are primarily responsible for overall field-related project activities (data quality and integration at all levels, resolving community issues), and training. Computer randomised list of enrolled children will be used by QC team for random household visits.

The QC team works in close coordination with the investigative team and provides regular feedback on quality issues. Quarterly meetings between QC team and senior investigative team are scheduled to discuss overall quality issues and related corrective measures to be undertaken.

Data management
Data are collected in real-time using either tablets or laptop computers. Each site uses an in-house designed data management software with user friendly graphical user interface for data collection. Generic case report forms and data dictionary are used to maintain data consistency across sites. In-built range, logical and skipping pattern will ensure data quality and integrity. The database is password protected with restricted access. Each user is assigned a unique user identifier to access the software and an audit trial is maintained for database operations. The centralised server located at each site synchronises the data on daily basis. Data are shared monthly with WHO data quality monitoring team
who is responsible for data quality checks and provide feedback to sites. They generate query forms which are returned to the study sites for verification.

Data security and storage
A backup of the data is kept in the server at WHO protected by a specific password and accessible to only authorised users. An additional backup of the data is kept in a password-protected external hard drive at a site away from WHO at the recruiting site central offices.

Record retention and archival
All the study documents including participant's source data and documents will be archived by the study sites after the completion of the study, till the time WHO informs in writing to the study sites that they no longer need to maintain the study documents.

Outcome measures
The primary efficacy outcomes are 1) the percentage of enrolled children who have duration of diarrhoea of >5 days, 2) the mean number of loose or watery stools after enrolment and 3) the percentage of children vomiting within 30 min of administration of the zinc tablet.

Secondary outcomes of the trial include: i) proportion of children experiencing SAEs (life-threatening
or hospitalisation); ii) proportion with intermediate duration of diarrhoea (diarrhoea continuing beyond
3 days); iii) proportion of guardians with positive attitude towards treatment; iv) treatment adherence; v) mean serum plasma zinc concentration at days 1, 3, 7, 15, 21 and 30; vi) illness symptoms between day 15 and 60 after the treatment 2-week period prevalence and number of days with diarrhoea, fever or respiratory symptoms; vii) 60-day change in height/length, weight, MUAC, height/length-for-age z-score, weight-for-length/height z-score, weight-for-age z-score, MUAC z-score, stunting, wasting,
underweight; viii) adherence to regimen; ix) study dropouts; x) maternal report of ease in supplement administration; xi) maternal report of child acceptability; xii) maternal recommendation of use for other children; xiii) maternal report of change in child skin condition, child appetite, activity levels, mood and diarrhoea severity.

Statistical analysis
All primary analyses of non-inferiority tests will be conducted on the principle of intention-to-treat (ITT).

All non-inferiority margins will be defined a priori. We will also conduct sensitivity analyses using a per-protocol (PP) approach.15 The analysis population for the ITT approach will include all randomised patients with assessable data, regardless of whether the participant is known to have received a full 14-day dose of zinc or not. The analysis population for the PP approach will include study participants who are documented to have taken zinc supplementation for the first 5 days after randomization
regardless if they vomited the dose. The PP definition was selected due to the primary outcome being
diarrhoea duration >5 days. Descriptive statistics will be used to summarise background demographic and baseline clinical characteristics by trial arm.

Analysis of primary outcomes

Primary outcome 1
Number (%) of subjects with diarrhoea episodes >5 days. The last day of diarrhoea will be defined as the day in which there is passage of the last liquid or semi-liquid stool prior to two diarrhoea-free days (days when less than three loose stools/day). The duration of diarrhoea will be defined as the number of days between randomisation (not the reported day of onset of diarrhoea symptoms before randomisation) and the last day with diarrhoea. Children who are lost to follow-up, die or withdraw before 5 days will be excluded from this analysis. For the primary analysis, we have set the threshold for non-inferiority of lower doses of zinc (10 or 5 mg/day) as compared with the standard 20 mg/day at <4% in absolute risk (risk difference) compared with the standard dose in the proportion of subjects with prolonged diarrhoea. The proportions of participants with a prolonged diarrhoea episode (defined as >5 days) will be calculated in all treatment arms, and the risk differences (and their 95% CIs) between the lower doses (5 and 10 mg/day) and the standard dose (20 mg) will be estimated. A Cochran-Mantel-Haenszel approach will be used to take stratifying randomisation factors, for example, country and age groups, into account. If the upper limit of the 95% CI for the risk difference is <4%, we will conclude non-inferiority for one or both lower dose arms. We will also examine the RR of prolonged diarrhoea episodes in both lower dose arms compared with the standard dose arm using RR regression
which accounts for factors included in the stratified randomisation. In secondary analyses, Cox proportional hazard models will be used to estimate HRs and their 95% CIs for recovery from diarrhoea in each of the lower dose arms compared with the standard dose arm. The time to recovery is defined as the duration of diarrhoea as noted above.

Primary outcome 2
Total number of loose or watery stools after enrolment. An analysis of covariance (ANCOVA) approach will be used to estimate the mean differences and their 95% CI in the total number of loose or watery stools after enrolment for each lower dose arm compared with the standard dose arm, while accounting for the stratified randomisation design. The non-inferiority margin was set at two stools, therefore if the upper limit of the 95% CI is less than two stools, we will reject the null hypothesis that the lower dose zinc is inferior to the standard dose in terms of reducing the total number of loose or watery stools.

Primary outcome 3
Vomiting within 30 min after administration of the trial regimen. We hypothesise that the lower dose of zinc will be associated with a reduced risk of vomiting and therefore a superiority test will be

used. Vomiting within 30 min of each daily zinc dose is repeatedly measured during the 14-day administration period. Generalised estimating equations (GEE) with the log link, binomial variance and exchangeable correlation matrix will be used to assess the RR of vomiting among the three treatment arms. The
exchangeable working covariance matrix and robust estimators of the variances will be used to construct CIs. The robust estimators are consistent estimators of the variances even if the working correlation matrix is misspecified. Stratified randomisation factors will be considered in the model. A secondary analysis concerning severe vomiting (defined as vomiting requiring hospitalization or vomiting requiring intravenous fluids) will also be performed in similar fashions. We will also examine the proportion of children ever vomiting between the treatment arms and examine whether the RR of vomiting differs by follow-up day.

Analysis of change in plasma zinc and other secondary outcomes
Due to the sampling design of participants having paired blood sampled on three schedules (days 1 and 15; days 3 and 21; days 7 and 30), we will assess the effect of the randomised zinc regimen at both the population level and individual level. For the analysis of population-level zinc, we will use a mixed model approach to compare patterns of plasma zinc concentrations over time between the randomised
treatment arms. The main exposure variables in the model will include treatment arm, study day and an interaction term between treatment arm and study day. In case there is not a linear relationship between study day and plasma zinc concentrations, restricted cubic splines will be used to examine the non-linear relationship between these two variables. The interaction term between zinc dose and study day in the model measures whether the trajectory of plasma zinc differs by zinc supplementation over the full period. If the overall test for this interaction term is statistically significant, group means at each assessment day will then be compared using least-square means with the Tukey-Kramer adjustment. To be consistent with our stratified randomisation study design, stratification factors will be included in the model.

For all other secondary outcomes (see clinicaltrial.gov NCT03078842), we will use approaches similar to
the primary analyses, including an ANCOVA approach for non-repeated continuous outcomes, RR regression for non-repeated binomial outcomes and GEE or mixed effect models for repeated longitudinal outcomes.

Sensitivity analyses and modification of treatment effect
Although randomisation is designed such that, on average, treatment groups will be balanced with respect to all baseline prognostic factors, this may not be true in all cases. As a result, we will re-assess treatment effects as observed in the original analysis after adjusting for factors that are potentially imbalanced across randomised arms. If imbalance occurs, we will compare and present the
results for both unadjusted and adjusted analyses. In addition, the study was not designed to detect effect modification of the treatment effect among subgroups of children. As a result, we acknowledge that we are likely underpowered to detect differences in the magnitude of a treatment effect among subgroups unless there is strong effect modification. The potential baseline effect modifiers we plan to explore include: study site (India/Tanzania), child age (<12 vs >12 months), child sex (male vs female), prior receipt of rotavirus vaccine (yes vs no), maternal HIV status (yes vs

no), dysentery at enrolment (yes vs no), baseline dehydration status (yes vs no), baseline axillary temperature (<38°C vs >38°C),
baseline respiratory rate, recent antibiotic use (yes vs no), intercurrent illness (cough, difficulty breathing or earache), current breastfeeding status (yes vs no) and prior breastfeeding status (yes vs no). Additional variables that we will test for effect modification will include child anthropometric measures (length/height for age, weight for age and weight for length/height z-scores and MUAC), family socioeconomic status (<median wealth index, >median wealth index), maternal education, household water quality (improved vs unimproved), household sanitation quality (improved vs unimproved), baseline plasma zinc levels (<median, >median) and trial regimen adherence (<median, >median). Factor analysis will be used to derive wealth index from family possession variables. WHO/Unicef Joint Monitoring Programme definitions will be used to clarify improved versus unimproved for the household water quality and sanitation.16

Monitoring

Data and Safety Monitoring Board
A Data Safety and Monitoring Board (DSMB) has been established to monitor SAEs and to review the statistical analysis plan and associated stopping rules for benefit, futility or harm determined using O'Brien-Fleming stopping boundaries. The DSMB includes five members with expertise in clinical trials, statistics, child mortality assessment, paediatric care in resource-limited settings or practical experience from each study country. The DSMB meets electronically or in person at least every 6 months. SAEs related to study participation are monitored in realtime, are summarised and reported to study investigators, WHO and relevant institutional review boards (IRBs) within 24 hours of notification in India and 72 hours of notification in Tanzania. Both sites are required to report to WHO within 72 hours of notification. Frequencies and descriptions of SAEs are pooled each month by the data management team at WHO and circulated to investigators, DSMB and IRBs. When more than half of the person-time is accrued in the study, the DSMB will review an interim data analysis by arm to determine whether
stopping boundaries have been crossed.

Auditing
The sites are responsible for internal quality checks. WHO coordinators conduct at least one or two site monitoring visits per year to each site.

Discussion
Zinc supplementation in children during episodes of diarrhoea results in several advantages as described
earlier.1 7 12 Dose recommendations from WHO/Unicef were primarily based on previous clinical studies of zinc treatment of diarrhoea that used these amounts of zinc. Moreover, because zinc is absorbed less efficiently during diarrhoea,17 it has been assumed that the therapeutic dose for treatment of diarrhoea should be substantially greater than the RDA for zinc (3–5 mg/day for children
aged <5 years), depending on bioavailability from the usual diet.9 Therefore, ZTDT was designed to examine the optimal therapeutic dose of zinc supplementation for children aged under 5 with acute diarrhoea in a south Asian country and a sub-Saharan African country. A recent search of clinicaltrials. gov found no other clinical trials that are determining an optimal zinc therapeutic dose for children with acute diarrhoea. An additionalsearch on PubMed, Google Scholar and other search

engines was carried out where it was noted that one study was found to determine the optimal dose of zinc supplementation in diarrhoea.18 The double-blind randomised trial was carried out using 10 or 20 mg zinc sulfate versus placebo. No difference in duration nor frequency of diarrhoea was noted. However, this study was carried out in Switzerland, where the epidemiology of acute childhood diarrhoea is different than in India or Tanzania. As a result, ZTDT will likely be the first randomised trial in low-resource settings to determine the optimal dose of therapeutic zinc in children with acute diarrhoea.

Overall, the ZTDT study will measure important clinical outcomes (outcome of diarrhoea on growth, frequency of vomiting) in a large number of children under 5 years being treated for acute diarrhoea in India and Tanzania. It will also provide evidence for the effect of zinc on plasma zinc concentrations over several days after supplementation, the effect of zinc on post-illness outcomes as well as the acceptability of zinc supplementation. The trial results will be communicated in academic
journals and at the national and local levels in Tanzania and India through policy briefs and dissemination meetings. The results of ZTDT will likely be generalisable to children under 5 years with acute diarrhoea in similar resource-limited settings and as such will have global relevance. The findings will be an important consideration in any further revision of the WHO technical guidelines on
diarrhoea case management.

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Contributors

All the authors participated in conceptualisation, design, sample size calculations and writing of the analysis plan for the study. Two workshops held at WHO to develop joint harmonised SOP and CRFs for the study in which all the authors contributed. SSS and PD prepared the first draft of the paper. All authors contributed to revisions of the manuscript and contributed to the revision of the final draft of the manuscript. All the authors have read and approved the final manuscript.

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Competing interests
None declared.

Patient consent for publication
Not required.

Ethics approval
The ZTDT protocol has been approved by WHO ethics committee (reference no. ERC.0002738), Boston Children's Hospital IRB (reference no .IRB-P00024269), Tanzania Food and Drug Authority (reference no. TFDA0016/CTR/0015/03), the Tanzanian National Institute of Medical Research (reference no. NIMR/HQ/R.8a/Vol.IX/2333) and Muhimbili University of Health and Allied Sciences, Dar es Salaam (reference no. 2016-10-31/AEC/Vol.XI/314) and IEC of Subharti Medical College & Hospital, Meerut, Uttar Pradesh, India (reference no. SMC/EC/2016/84) (see online supplementary additional file 4). All participants will be asked to provide written informed consents before trial enrolment. Caregivers
who consent for the trial will also be asked for consent to be escorted back to their home to register the address, to contact the participant and to be visited at home or followed at home if the participant misses the clinic visit, as well as to store and use all data and child blood samples for this study and future research studies.

Provenance and peer review
Not commissioned; internally peer reviewed.

Data sharing statement
Full protocol is being published in a peer-reviewed open access journal. Additional information about the protocol/SOPs will be available on request. In addition, a commitment is made by the investigators: 1) to use data for research purposes and not to identify individual participants and 2) to use appropriate technology to secure the data. Consistent with WHO policies and practice, each site owns the data they generate from the national populations they serve. Sites voluntarily agree to share the data with WHO as the ZTDT Coordinating Body and share the final 'frozen data set' with BMGF for their internal use.

Author note
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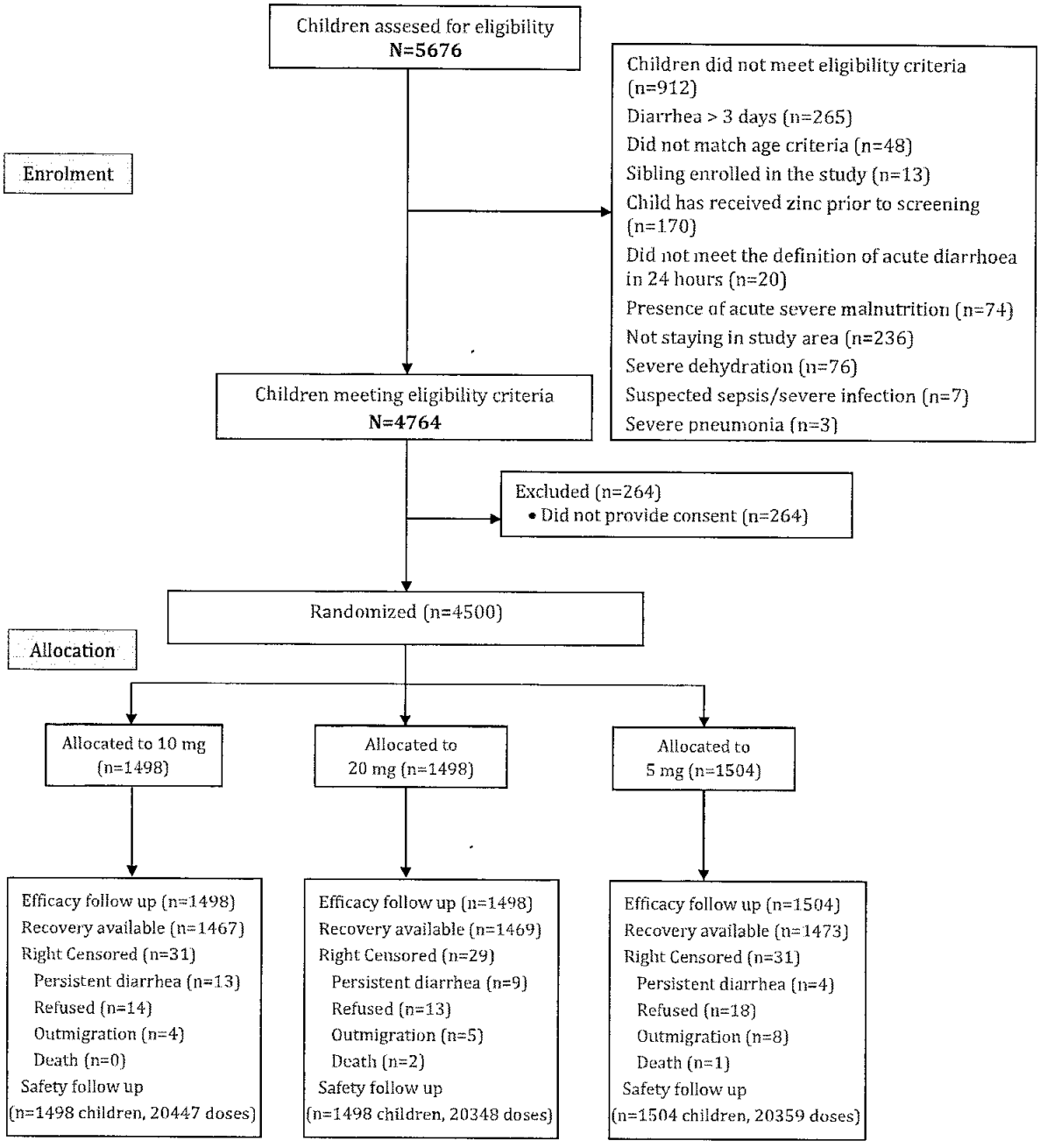
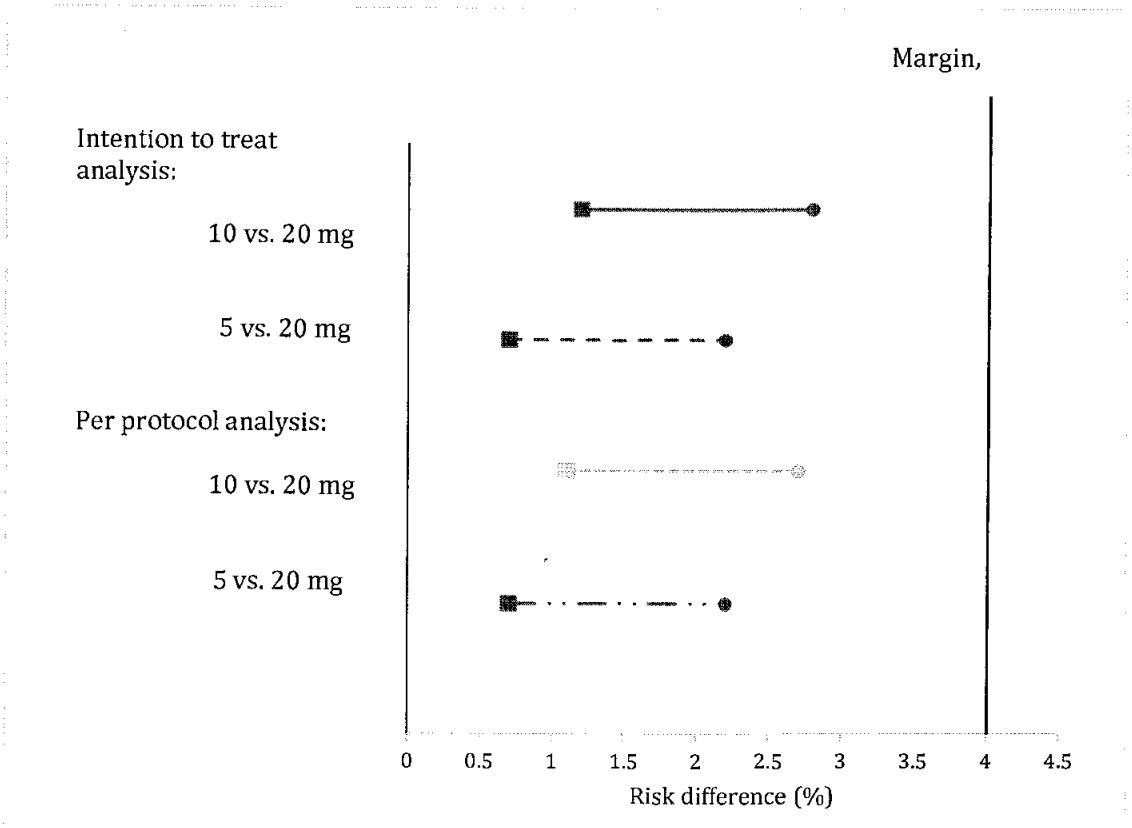
Supplementary Figures

Supplementary Figure 1: Study Flow Diagram

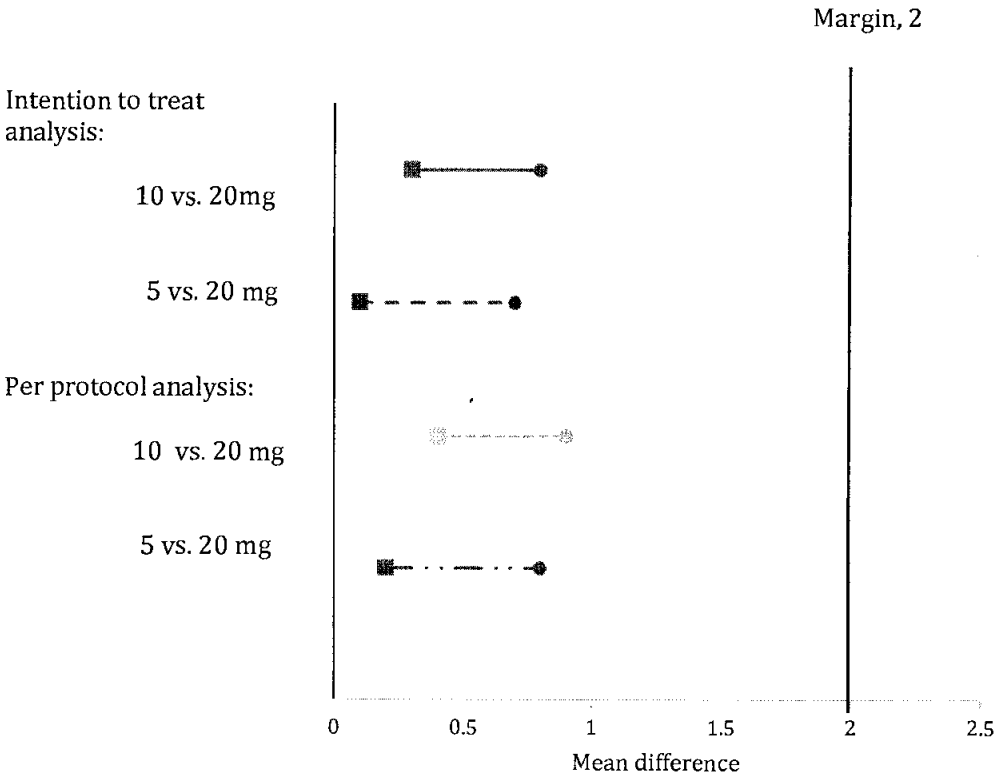
Figure 1: Study Flow Diagram



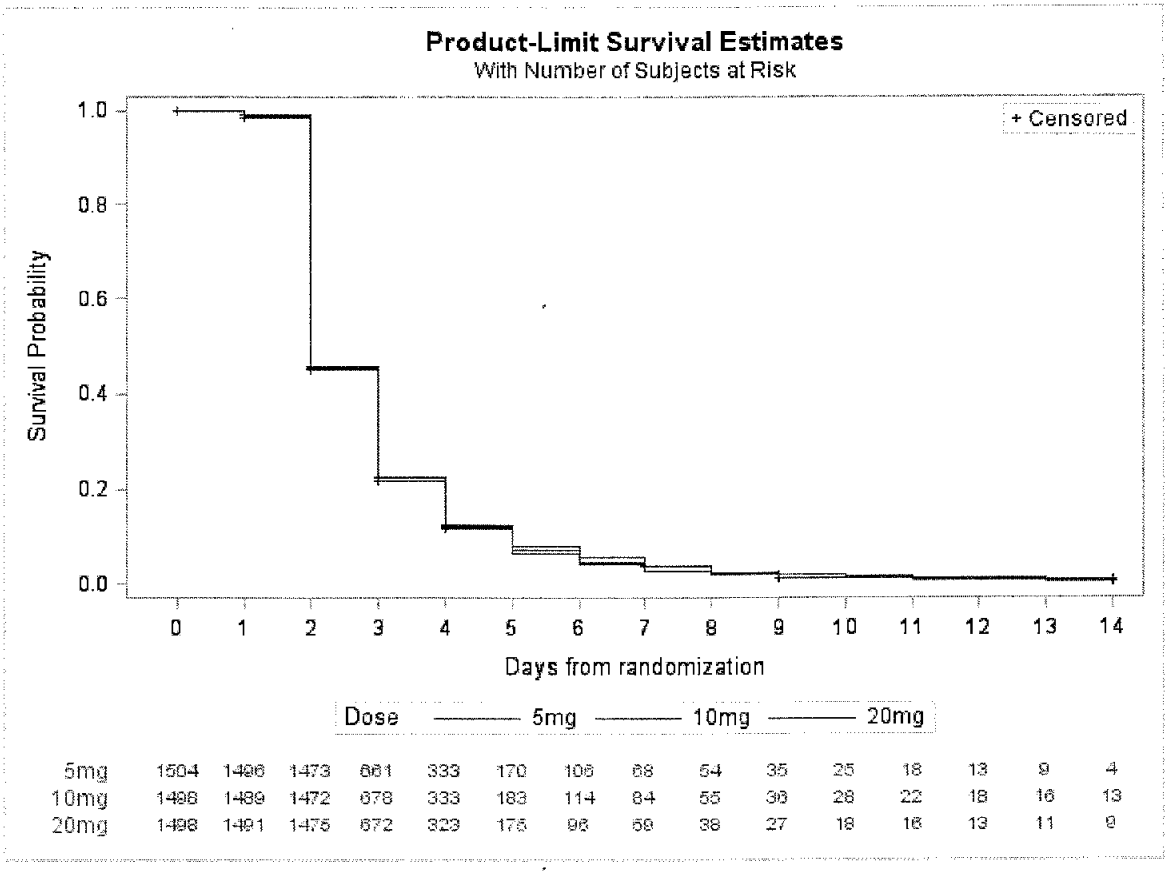
Supplementary Figure 2. Forest plot for differences in proportion of children with diarrhea duration > 5 days. Absolute differences (■) and upper 95% confidence intervals (•) between low dose and standard dose arms. The non-inferiority margin was defined a priori at 4.0%. In none of the performed analyses was the non-inferiority margin exceeded.



Supplementary Figure 3. Forest plot for differences in mean number of total loose or watery stools. Absolute differences (■) and upper 95% confidence intervals (•) between low dose and standard dose arms. The non-inferiority margin was defined a priori at 2 stools. In none of the performed analyses was the non-inferiority margin exceeded.



Supplementary Figure 4. Kaplan-Meier Curve for time to initial diarrhea episode recovery by zinc supplementation dose



Supplementary Tables

Supplementary Table 1. Additional baseline characteristics of the trial population stratified by zinc supplementation dose (n=4500)*

	5 mg (N=1504) Mean ± SD or n (%)	10 mg (N=1498) Mean ± SD or n (%)	20 mg (N=1498) Mean ± SD or n (%)
Maternal and household characteristics			
No maternal education[1]	257 (17.3)	254 (17.1)	230 (15.5)
Improved water[2]	1485 (99.1)	1485 (99.3)	1485 (99.3)
Improved sanitation[3]	1486 (99.1)	1488 (99.5)	1489 (99.5)
Child characteristics			
Height (cm)	79.9 ± 11.0	79.7 ± 11.0	80.1 ± 11.7
Weight (kg)	10.0 ± 2.5	9.9 ± 2.5	10.0 ± 2.7
MUAC (cm)	14.1 ± 1.2	14.0 ± 1.2	14.1 ± 1.2
Stunted (LAZ/HAZ < -2)	424 (28.2)	382 (25.5)	382 (25.5)
Wasted (WLZ/WHZ < -2	131 (8.7)	135 (9.0)	141 (9.4)
Underweight (WAZ < -2)	353 (23.5)	348 (23.2)	333 (22.2)

*The values shown are based on available data. Information was available for all participants for all variables except 45 were missing maternal education, 9 were missing sanitation, and 9 were missing water quality. LAZ/HAZ denotes length/height-for-age z-score, WLZ/WHZ weight-for-length/height z-score, WAZ weight-for-age z-score, and MUAC mid-upper arm circumference.

[1]Never attained formal education
[2] WHO/UNICEF Joint Monitoring Programme definition that included piped water, boreholes or tubewells, protected dug wells, protected springs, rainwater, and packaged or delivered water https://washdata.org/monitoring/drinking-water (accessed May 24, 2020)
[3] WHO/UNICEF Joint Monitoring Programme definition that included flush/pour flush to piped sewer system, septic tanks or pit latrines; ventilated improved pit latrines, composting toilets or pit latrines with slabs https://washdata.org/monitoring/sanitation (accessed May 24, 2020)

Supplementary Table 2. Baseline characteristics of the India trial population stratified by zinc supplementation dose (n=2250)

	5 mg (N=751) Mean ± SD or n (%)	10 mg (N=749) Mean ± SD or n (%)	20 mg (N=750) Mean ± SD or n (%)
Maternal and household characteristics			
Maternal age, years	26.4 ± 4.2	26.4 ± 4.0	26.3 ± 3.9
Maternal education, years	6.6 ± 5.0	6.5 ± 4.9	6.8 ± 4.7
No maternal education	219 (29.2)	214 (28.6)	188 (25.1)
Improved water[1]	736 (98.7)	739 (98.9)	741 (99.1)
Improved sanitation[2]	743 (99.6)	747 (100.0)	747 (99.9)
Household wealth above median[1]	379 (50.8)	370 (49.5)	371 (49.6)
Child characteristics			
Age at randomization (months)	26.6 ± 16.2	26.4 ± 16.4	27.0 ± 17.0
Age at randomization			
6 to <12 months	171 (22.8)	180 (24.0)	193 (25.7)
12 to <24 months	207 (27.6)	199 (26.6)	186 (24.8)
24 to <60 months	373 (49.7)	370 (49.4)	371 (49.5)
Female	354 (47.1)	374 (49.9)	362 (48.3)
Breastfeeding day prior to enrollment	422 (56.6)	406 (54.4)	402 (53.8)
Rotavirus vaccination	1 (0.1)	0 (0.0)	2 (0.3)
Duration of diarrhea before enrollment			
≤ 24 hours	34 (4.5)	28 (3.7)	33 (4.4)
25 to 48 hours	697 (92.8)	695 (92.8)	686 (91.5)
49 to <72 hours	20 (2.7)	26 (3.5)	31 (4.1)
Number of loose or watery stools in the 24 hours before enrollment	6.4 ± 2.1	6.4 ± 2.2	6.4 ± 2.1
Dysentery	11 (1.5)	17 (2.3)	19 (2.5)
Some dehydration*	3 (0.4)	0 (0.0)	3 (0.4)
Axillary temperature >38°C	13 (1.7)	9 (1.2)	10 (1.3)
Cough or difficulty breathing	279 (37.2)	312 (41.7)	281 (37.5)
Observed respiratory rate >40 bpm	12 (1.6)	10 (1.3)	6 (0.8)
Prior antibiotic use	32 (2.1)	26 (1.7)	38 (2.5)
Height (cm)	81.5 ± 12.0	81.4 ± 12.2	82.0 ± 13.0
Weight (kg)	10.1 ± 2.7	10.1 ± 2.7	10.2 ± 3.0
MUAC (cm)*	13.7 ± 1.2	13.7 ± 1.1	13.8 ± 1.2
Mean LAZ/HAZ	-1.7 ± 1.2	-1.6 ± 1.1	-1.6 ± 1.2
Mean WLZ/WHZ	-0.9 ± 0.9	-0.9 ± 0.9	-0.9 ± 0.9

Mean WAZ*	-1.6 ± 1.0	-1.5 ± 0.9	-1.5 ± 1.0
Mean MUACZ	-1.3 ± 0.9	-1.2 ± 0.9	-1.2 ± 0.9
Stunted (LAZ/HAZ < -2)*	307 (40.9)	258 (34.5)	257 (34.3)
Wasted (WLZ/WHZ < -2*	89 (11.9)	84 (11.2)	93 (12.4)
Underweight (WAZ < -2)	270 (36.0)	234 (31.2)	234 (31.2)
Zinc dose (mg/kg body weight)	0.53 ± 0.14	1.07 ± 0.28	2.13 ± 0.62
Plasma zinc concentration (µg/dL)[2]	80.7 ± 22.1	81.8 ± 22.1	82.9 ± 22.9
Plasma zinc concentration <65 µg/dL[3]	58 (24.9)	48 (19.9)	61 (23.2)

* Definitions: LAZ/HAZ denotes length/height-for-age z-score, WLZ/WHZ weight-for-length/height z-score, WAZ weight-for-age z-score, and MUAC mid-upper arm circumference.
WHO Integrated Management of Childhood Illness (IMCI) some dehydration definition requires two of the following signs: restless, irritable; sunken eyes; drinks eagerly, thirsty; skin pinch goes back slowly.
[1] WHO/UNICEF Joint Monitoring Programme definition that included piped water, boreholes or tubewells, protected dug wells, protected springs, rainwater, and packaged or delivered water https://washdata.org/monitoring/drinking-water (accessed May 24, 2020)
[2] WHO/UNICEF Joint Monitoring Programme definition that included flush/pour flush to piped sewer system, septic tanks or pit latrines; ventilated improved pit latrines, composting toilets or pit latrines with slabs https://washdata.org/monitoring/sanitation (accessed May 24, 2020)

[1]Country-specific household wealth index was constructed using a principal component analysis of household ownership, household assets, drinking water source, and sanitation
[2] Plasma zinc concentrations were assessed in a random sample of 33% of participants at baseline at each site

Supplementary Table 3. Baseline characteristics of Tanzania trial population stratified by zinc supplementation dose (n=2250)

	5 mg (N=753) Mean ± SD or n (%)	10 mg (N=749) Mean ± SD or n (%)	20 mg (N=748) Mean ± SD or n (%)
Maternal and household characteristics			
Maternal age, years	27.0 ± 5.6	27.2 ± 5.7	27.5 ± 5.9
Maternal education, years	8.0 ± 3.0	7.7 ± 2.9	7.8 ± 3.0
No maternal education	38 (5.2)	40 (5.4)	42 (5.7)
Improved water*	749 (99.5)	746 (99.6)	744 (99.5)
Improved sanitation*	743 (98.7)	741 (98.9)	742 (99.2)
Household wealth above median[1]	381 (50.6)	368 (49.1)	401 (53.6)
Child characteristics			
Age at randomization (months)	19.4± 12.3	19.0 ± 11.3	19.4 ± 12.2
Age at randomization			
6 to <12 months	241 (32.0)	230 (30.7)	241 (32.2)
12 to <24 months	292 (38.8)	303 (40.5)	290 (38.8)
24 to <60 months	220 (29.2)	216 (28.8)	217 (29.0)
Female	357 (47.4)	351 (46.9)	357 (47.7)
Breastfeeding day prior to enrollment	454 (60.3)	451 (60.2)	451 (60.3)
Rotavirus vaccination	748 (99.5)	746 (100.0)	741 (98.9)
Duration of diarrhea before enrollment			
≤ 24 hours	24 (3.2)	20 (2.7)	26 (3.5)
25 to 48 hours	562 (74.6)	529 (70.6)	545 (72.9)
49 to <72 hours	167 (22.2)	200 (26.7)	177 (23.7)
Number of loose or watery stools in the 24 hours before enrollment	6.4 ± 2.1	6.4 ± 2.2	6.4 ± 2.1
Dysentery	43 (5.7)	45 (6.0)	32 (4.3)
Some dehydration*	29 (3.9)	11 (1.5)	10 (1.3)
Axillary temperature >38°C	35 (4.7)	31 (4.1)	24 (3.2)
Cough or difficulty breathing	126 (16.7)	143 (19.1)	126 (16.8)
Observed respiratory rate >40 bpm	74 (9.8)	78 (10.4)	75 (10.0)
Prior antibiotic use	28 (3.7)	31 (4.1)	20 (2.7)
Height (cm)	78.3 ± 9.6	77.9 ± 9.4	78.2 ± 9.9
Weight (kg)	9.8 ± 2.2	9.6 ± 2.1	9.8 ± 2.3
MUAC (cm)*	14.5 ± 1.1	14.3 ± 1.1	14.4 ± 1.1
Mean LAZ/HAZ	-0.9 ± 1.1	-1.0 ± 1.0	-1.0 ± 1.1

Mean WLZ/WHZ	-0.4 ± 1.1	-0.5 ± 1.1	-0.4 ± 1.1
Mean WAZ	-0.8 ± 1.0	-0.9 ± 1.0	-0.8 ± 1.1
Mean MUACZ	-0.3 ± 0.9	-0.4 ± 0.9	-0.4 ± 0.9
Stunted (LAZ/HAZ < -2)*	117 (15.5)	124 (16.6)	125 (16.7)
Wasted (WLZ/WHZ < -2*	42 (5.6)	51 (6.8)	48 (6.4)
Underweight (WAZ < -2)*	83 (11.0)	114 (15.2)	99 (13.2)
Zinc dose (mg/kg body weight)	0.53 ± 0.11	1.08 ± 0.22	2.15 ± 0.45
Plasma zinc concentration (µg/dL)[2]	60.9 ± 20.0	66.3 ± 23.3	60.7 ± 27.5
Plasma zinc concentration <65 µg/dL	117 (57.6)	95 (49.7)	113 (63.5)

* Definitions: LAZ/HAZ denotes length/height-for-age z-score, WLZ/WHZ weight-for-length/height z-score, WAZ weight-for-age z-score, and MUAC mid-upper arm circumference.
WHO Integrated Management of Childhood Illness (IMCI) some dehydration definition requires two of the following signs: restless, irritable; sunken eyes; drinks eagerly, thirsty; skin pinch goes back slowly.
WHO/UNICEF Joint Monitoring Programme definition that included piped water, boreholes or tubewells, protected dug wells, protected springs, rainwater, and packaged or delivered water https://washdata.org/monitoring/drinking-water (accessed May 24, 2020)
WHO/UNICEF Joint Monitoring Programme definition that included flush/pour flush to piped sewer system, septic tanks or pit latrines; ventilated improved pit latrines, composting toilets or pit latrines with slabs https://washdata.org/monitoring/sanitation (accessed May 24, 2020)

[1]Country-specific household wealth index was constructed using a principal component analysis of household ownership, household assets, drinking water source, and sanitation
[2] Plasma zinc concentrations were assessed in a random sample of 33% of participants at baseline at each site

Supplementary Table 4. Subgroup analysis for results on proportion of children with diarrhea >5 days (primary outcome 1)

Potential effect modifier (baseline characteristic)	Risk Difference 95% CI (5mg vs 20mg)[1]	Risk Difference 95% CI (10mg vs 20mg)[2]
Study site		
India	0.0%(-2.7%, 2.8%)	1.1%(-1.8%, 3.9%)
Tanzania	1.3%(-1.0%, 3.7%)	1.4% (-1.0%, 3.7%)
Age group		
<12 month	-1.0%(-5.5%,3.5%)	0.7%(-3.9%,5.4%)
≥12 months	1.5%(-0.3%,3.3%)	1.6%(-0.2%,3.4%)
Sex		
Male	0.6%(-2.0%,3.2%)	2.0%(-0.7%,4.8%)
Female	0.8%(-1.8%,3.3%)	0.3%(-2.2%,2.8%)
Rotavirus vaccine received		
No	0.0%(-2.8%,2.8%)	1.0%(-1.9%,3.8%)
yes	1.4%(-1.0%,3.7%)	1.4%(-0.9%,3.8%)
Maternal HIV status		
No	1.3%(-1.1%,3.7%)	1.7%(-0.7%,4.2%)
Yes	n.e.	n.e.
Dysentery		
No	1.1%(-0.8%,2.9%)	1.3%(-0.6%,3.1%)
Yes	-8.7%(-20.3%,2.8%)	0.2%(-12.9%,13.4%)
Dehydration		
no	0.5%(-1.3%,2.3%)	1.1%(-0.7%,3.0%)
Yes	8.4%(-11.0%,27.9%)	14.5%(-16.3%,45.3%)
Axillary temp >38°C		
No	0.6%(-1.2%,2.4%)	1.4%(-0.5%,3.2%)
yes	1.5%(-15.1%,18.2%)	-5.2%(-20.5%,10.2%)
Respiratory rate > 40 /min		
no	0.4%(-1.5%,2.3%)	0.8%(-1.1%,2.7%)
yes	5.0%(-2.3%,12.2%)	8.9%(0.7%,17.2%)
Recent antibiotic use		
No	0.6%(-1.3%,2.4%)	1.2%(-0.6%,3.1%)
Yes	5.2%(-7.7%,18.1%)	1.1%(-9.6%,11.8%)

[1] Risk Difference > 0 means proportion of children with diarrhea > 5 days was greater in 5mg group
[2] Risk Difference > 0 means proportion of children with diarrhea > 5 days was greater in 10mg group

Breastfed		
No	1.8%(-0.2%,3.9%)	2.2%(0.1%,4.2%)
Yes	-0.8%(-4.1%,2.4%)	-0.1%(-3.4%,3.3%)
Stunted		
No	1.2%(-1.0%,3.3%)	1.5%(-0.6%,3.7%)
Yes	-0.7%(-4.2%,2.8%)	0.3%(-3.4%,4.0%)
Underweight		
No	0.4%(-1.7%,2.4%)	1.5%(-0.6%,3.6%)
Yes	1.6%(-2.5%,5.8%)	0.2%(-3.8%,4.1%)
Wasted		
No	0.8%(-1.1%,2.7%)	1.4%(-0.6%,3.3%)
yes	-1.0%(-7.3%,5.3%)	-0.5%(-6.8%,5.9%)
MUAC less than 125 mm		
No	1.4%(-0.5%,3.2%)	1.9%(0.1%,3.8%)
Yes	-7.6%(-15.9%,0.7%)	-7.3%(-15.5%,1.0%)
Family wealth < median		
No	0.2%(-2.2%,2.6%)	2.6%(-0.02%,5.2%)
Yes	1.1%(-1.6%,3.9%)	-0.0%(-2.8%,2.5%)
Maternal education years < 8		
No	1.5%(-1.4%,4.4%)	2.1%(-0.9%,5.1%)
Yes	0.1%(-2.2%,2.5%)	0.7%(-1.6%,3.1%)
HH water quality (improved vs. unimproved)		
No	n.e.	n.e.
Yes	0.6%(-1.2%,2.5%)	1.1%(-0.8%,2.9%)
HH sanitation quality (improved vs. unimproved)		
No	0.6%(-1.2%,2.5%)	1.1%(-0.7%,2.9%)
Yes	0.7%(-1.1%,2.5%)	1.2%(-0.6%,3.1%)
Baseline plasma zinc <65 µg/dL		
No	-2.9%(-7.4%,1.6%)	-3.4%(-7.8%,0.9%)
Yes	4.5%(-1.2%,10.2%)	4.9%(-1.3%,11.1%)

n.e.: Not estimable due to no child having diarrhea duration >5 days in the subgroup

Supplementary Table 5. Subgroup analysis for results on total number of stools (primary outcome 2)

Potential effect modifier (baseline characteristic)	Mean Difference 95% CI (5mg vs 20mg)[3]	Mean Difference 95% CI (10mg vs 20mg)[4]
Study site		
India	0.1 (-1.0, 1.1)	0.3 (-0.7, 1.4)
Tanzania	0.1 (-0.6, 0.9)	0.2 (-0.6, 1.0)
Age group		
<12 month	0.1(-1.6, 1.8)	0.8(-0.9, 2.6)
≥12 months	0.2(-0.4, 0.7)	0.1(-0.5, 0.7)
Sex		
Male	-0.2(-1.1, 0.8)	0.3(-0.6, 1.3)
Female	0.3(-0.5, 1.2)	0.2 (-0.7, 1.0)
Rotavirus vaccine received		
No	0.0(-1.0,1.1)	0.3(-0.8,1.3)
yes	0.1(-0.6,0.9)	0.2(-0.5,1.0)
Maternal HIV status		
No	0.1(-0.6,0.9)	0.3(-0.5,1.0)
Yes	0.2(-3.8,4.3)	-2.0(-6.4,2.4)
Dysentery		
No	0.1(-0.6,0.7)	0.1(-0.5,0.8)
Yes	0.3(-3.9,4.5)	3.5(-0.6,7.5)
Dehydration		
no	0.0(-0.6,0.7)	0.2(-0.4,0.9)
Yes	2.7(-4.9,10.4)	7.6(-2.5,17.6)
Axillary temp >38°C		
No	0.1(-0.6,0.7)	0.3(-0.3,1.0)
yes	-0.8(-5.4,3.7)	-2.0(-6.6,2.7)
Respiratory rate > 40 /min		
no	-0.0(-0.7,0.6)	0.1(-0.6,0.8)
yes	1.7(-0.8,4.1)	3.1(0.7,5.6)
Recent antibiotic use		
No	0.1(-0.6,0.7)	0.2(-0.4,0.9)
Yes	1.6(-2.5,5.7)	1.4(-2.5,5.4)

[3] Mean Difference>0 means number of stools was higher in the 5mg group
[4] Mean Difference>0 means number of stools was higher in the 10mg group

Breastfed		
No	0.5(-0.4,1.2)	0.5(-0.2,1.3)
Yes	-0.4(-1.5,0.8)	-0.1(-1.3,1.0)
Stunted		
No	0.1(-0.7,0.8)	0.2(-0.5,1.0)
Yes	0.1(-1.1,1.3)	0.4(-0.9,1.6)
Underweight		
No	-0.1(-0.8,0.7)	0.3(-0.4,1.0)
Yes	0.5(-1.0,1.9)	0.1(-1.4,1.6)
Wasted		
No	0.1(-0.6,0.7)	0.2(-0.4,0.9)
yes	0.1(-2.9,3.0)	0.9(-2.0,3.8)
MUAC less than 125 mm		
No	0.1(-0.5,0.8)	0.4(-0.3,1.0)
Yes	-0.9(-3.8,2.0)	-1.4(-4.3,1.5)
Family wealth < median		
No	0.0(-1.0,1.0)	-0.1(-1.1,0.9)
Yes	0.2(-0.6,1.0)	0.6(-0.2,1.4)
Maternal education years < 8		
No	0.1(-0.9,1.1)	0.4(-0.6,1.5)
Yes	0.1(-0.7,0.9)	0.2(-0.6,1.0)
HH water quality (improved vs. unimproved)		
No	-0.7(-6.6,5.2)	-0.5(-7.0,6.0)
Yes	0.1(-0.6,0.7)	0.3(-0.4,0.9)
HH sanitation quality (improved vs. unimproved)		
No	0.6(-5.4,6.7)	0.5(-6.0,6.9)
Yes	0.1(-0.6,0.7)	0.3(-0.4,0.9)
Baseline plasma zinc <65 µg/dL		
No	-0.7(-2.4,0.9)	-1.1(-2.7,0.5)
Yes	1.4(-0.6,3.4)	1.3(-0.8,3.3)

Supplementary Table 6. Subgroup analysis for results on vomiting (primary outcome 3)

Potential effect modifier (baseline characteristic)	Risk Ratio 95% CI (5mg vs 20mg)[5]	Risk Ratio 95% CI (10mg vs 20mg)[6]
Study site		
India	0.30 (0.20, 0.44)	0.52 (0.38, 0.72)
Tanzania	0.93 (0.77, 1.11)	0.96 (0.80, 1.14)
Age group		
<12 month	0.76 (0.61, 0.96)	0.72 (0.56, 0.91)
≥12 months	0.69 (0.55, 0.86)	0.89 (0.72, 1.09)
Sex		
Male	0.74 (0.59, 0.92)	0.74 (0.59, 0.93)
Female	0.68 (0.54, 0.87)	0.88 (0.70, 1.09)
Rotavirus vaccine received		
No	0.30 (0.20, 0.44)	0.52 (0.37, 0.71)
yes	0.93 (0.78, 1.11)	0.97 (0.81, 1.15)
Maternal HIV status		
No	0.94 (0.79, 1.13)	0.96 (0.80, 1.15)
Yes	1.32 (0.49, 3.58)	1.17 (0.38, 3.55)
Dysentery		
No	0.67 (0.57, 0.79)	0.79 (0.67, 0.93)
Yes	2.52 (1.07, 5.93)	1.51 (0.60, 3.80)
Dehydration		
no	0.69 (0.59, 0.82	0.80 (0.69, 0.94)
Yes	1.35 (0.44, 4.14)	1.18 (0.30, 4.72)
Axillary temp >38°C		
No	1.02 (0.42, 2.45)	1.21 (0.52, 2.84)
yes	0.70 (0.59, 0.83)	0.79 (0.68, 0.93)
Respiratory rate > 40 /min		
no	0.69 (0.58, 0.82)	0.79 (0.67, 0.93)
yes	0.99 (0.60, 1.62	0.97 (0.59, 1.60
Recent antibiotic use		
No	0.71 (0.60, 0.83)	0.80 (0.68, 0.93)
Yes	0.81 (0.38, 1.75)	0.91 (0.45, 1.85)

[5] Risk Ratio < 1 means vomiting was less frequent in the 5mg group
[6] Risk Ratio < 1 means vomiting was less frequent in the 10mg group

Breastfed		
No	0.63 (0.46, 0.85)	0.90 (0.69, 1.19)
Yes	0.76 (0.63, 0.92)	0.76 (0.63, 0.92)
Stunted		
No	0.79 (0.66, 0.95)	0.80 (0.67, 0.95)
Yes	0.47 (0.31, 0.70)	0.84 (0.60, 1.18)
Underweight		
No	0.78 (0.65, 0.93)	0.82 (0.69, 0.97)
Yes	0.45 (0.29, 0.69)	0.77 (0.54, 1.10)
Wasted		
No	0.72 (0.61, 0.85)	0.81 (0.69, 0.96)
yes	0.62 (0.34, 1.12	0.72 (0.42, 1.26)
MUAC less than 125 mm		
No	0.74 (0.63, 0.88)	0.84 (0.71, 0.99)
Yes	0.36 (0.18, 0.75)	0.47 (0.24, 0.90)
Family wealth < median		
No	0.59 (0.47, 0.74)	0.78 (0.64, 0.97)
Yes	0.88 (0.70, 1.12)	0.84 (0.66, 1.07)
Maternal education years < 8		
No	0.56 (0.43, 0.73)	0.79 (0.63, 1.01)
Yes	0.84 (0.68, 1.04)	0.81 (0.66, 1.01)
HH water quality (improved vs. unimproved)		
No	0.52 (0.11, 2.61)	1.33 (0.39, 4.62)
Yes	0.71 (0.61, 0.84)	0.80 (0.68, 0.94)
HH sanitation quality (improved vs. unimproved)		
No	1.62 (0.20, 12.78)	0.87 (0.07, 11.54)
Yes	0.71 (0.60, 0.83)	0.81 (0.69, 0.94)
Baseline plasma zinc <65 µg/dL		
No	0.67 (0.43, 1.04)	0.60 (0.39, 0.94)
Yes	0.60 (0.37, 0.97)	0.64 (0.39, 1.05)

Supplementary Table 7. Mean difference in plasma zinc concentrations (μg/dL) at baseline, Day 3, Day 7,

	5 mg plasma samples (n)	5 mg group Plasma zinc Mean ± SD (μg/dL)	Mean difference* (μg/dL) 5 mg group as compared to 20 mg group (95% CI)	10 mg plasma samples (n)	10 mg group Plasma zinc Mean ± SD (μg/dL)	Mean difference* (μg/dL) 10 mg group as compared to 20 mg group (95% CI)	20 mg plasma samples (n)	20 mg Group Plasma zinc Mean ± SD (μg/dL)
Baseline [Day 1]	436	71.5 ± 23.4	-2.5 (-5.8, 0.9)	432	74.9 ± 23.9	1.0 (-2.4, 4.4)	441	74.0 ± 27.1
Day 3 [Day 3-5]	391	84.1 ± 31.1	-14.9 (-20.0, -9.8)	379	93.9 ± 42.1	-5.1 (-11.0, 0.8)	397	99.0 ± 41.5
Day 7 [Day 6-11]	408	85.1 ± 29.9	-19.0 (-24.6, -13.5)	419	92.3 ± 37.3	-10.8 (-16.7, -5.0)	403	104.1 ± 48.3
Day 15 [Day 12 - 18]	370	79.7 ± 25.9	-10.7 (-15.4, -6.1)	361	82.6 ± 27.8	-7.8 (-12.6, -3.0)	385	90.5 ± 38.0
Day 21 [Day 19-25]	392	74.3 ± 21.3	-2.0 (-5.1, 1.2)	383	77.6 ± 25.1	1.4 (-2.1, 4.8)	382	76.3 ± 23.3
Day 30 [Day 26-45]	409	73.6 ± 21.7	-3.8 (-7.0, -0.7)	434	74.4 ± 22.7	-3.0 (-6.2, 0.2)	410	77.4 ± 24.5

Day 15, Day 21 and Day 30 for the 5 mg group and 10 mg group as compared to 20 mg group

*Mean difference and confidence intervals estimated from linear mixed-effects model

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