

Title: Identifying Risk Factors for Vomiting during Diarrhea: A Secondary Analysis of a Randomized Trial of Zinc Supplementation

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Abstract:**Objectives:**

Supplemental zinc during acute diarrhea reduces illness duration but also increases vomiting. In a recent trial, we found that children receiving lower daily doses of zinc (5 mg or 10 mg vs. 20 mg) had lower rates of vomiting with comparable stool output and duration of diarrhea. We performed a secondary analysis to identify sociodemographic and clinical factors associated with vomiting in children with acute diarrhea.

Methods

We performed a secondary data analysis of 4500 children aged 6-59 months with an acute episode of diarrhea (< 72 hours before enrollment) in a randomized, double-blind controlled trial in India and Tanzania. To identify clinically important risk factors for overall, regimen-related and regimen-unrelated vomiting, we created log-binomials models with relative risks (RRs) and 95% confidence intervals (CIs).

Results

The trial enrolled 4500 children of whom 1203 (26.7%) had any vomiting. After adjusting for multiple demographic and clinical characteristics, presence of dehydration (RR 1.45, CI 1.10 – 1.92), being underweight (RR 1.22, CI 1.05 – 1.41), receipt of the rotavirus vaccine (RR 1.89, CI 1.69 – 2.12), and household wealth above the median (RR 1.17, CI 1.07 – 1.29) were factors associated with an increased risk of vomiting. Older age and lower zinc dosing were associated with a lower risk of vomiting.

Conclusions

Young, underweight or dehydrated children are more likely to have concurrent vomiting with zinc supplementation. Identification of these factors may allow providers to better monitor such children, thus reducing the chances of recurrent dehydration or inadequate dietary intake.

What is known:

- Zinc supplementation during acute diarrhea improves outcomes but can lead to vomiting.
- Lower daily dose (5 or 10 mg vs. 20 mg) of zinc reduces vomiting rates.

What is new:

- Among 4500 children with acute diarrhea in India and Tanzania, vomiting was noted in more than one quarter.
- Children who were younger, dehydrated, underweight, had received the rotavirus vaccine, who had families with higher wealth or who received 20 mg zinc daily were all independently more likely to have vomiting during an episode of diarrhea.

Introduction:

Diarrheal illness is a significant cause of morbidity and mortality worldwide, ranking as the fifth leading cause of mortality for children younger than five years of age¹⁻³. Despite substantial improvements in diarrhea mortality rates following the introduction of oral rehydration solution in the 1960s and 70s, the current morbidity burden^{4,5} demonstrates an ongoing need for the development of new and revised treatment approaches^{6,7}. Since 2004, the World Health Organization and UNICEF have recommended supplemental zinc in children with diarrheal illness (20 mg per day of zinc for children older than 6 months for 10-14 days and 10 mg per day for infants under six months old)⁸ since supplemental zinc during acute diarrheal episodes has been found to reduce the duration of illness^{9,10} and the risk of persistent diarrhea^{10,11}. Adherence to this recommendation has been suboptimal, with under 50% treatment adherence estimated in a cohort in India¹².

Zinc, meanwhile, is a known gastric irritant. High-dose zinc ingestion can present with epigastric pain, nausea, and vomiting¹³. Zinc supplementation is associated with an increased risk of vomiting^{9,13,14}, complicating its utility during a diarrheal illness that may include vomiting as one of its symptoms. Notably, the dosages recommended by the WHO/UNICEF (10 mg/day for children under 6 months of age and 20 mg/day for children older) greatly exceed the US Recommended Dietary Allowances (RDAs) for zinc (2 mg/day for 0 – 6-month-olds, and 3 mg/day between 7 months and 3 years of age)¹⁵. A Cochrane review found with moderate certainty that zinc supplementation increased the risk of vomiting in children with acute diarrhea (RR = 1.57 [1.32 – 1.86] compared with placebo in 2605 subjects enrolled in 6 trials¹⁶).

We completed a randomized trial (the Zinc Therapeutic Dosing Trial (ZTDT) – NCT03078842) that determined that lower daily doses of zinc (5 mg and 10 mg) in children older than 6 months with acute diarrhea offered the advantages of a reduced risk of vomiting (relative risks of 0.71 and 0.81, respectively) but was non-inferior with respect to stool output and duration of diarrhea compared to the standard dose of 20 mg¹⁷. The ZTDT constituted a large multi-national cohort of children with diarrheal illness who were closely monitored during zinc supplementation and follow-up. We hypothesized that risk factors for vomiting beside the receipt of supplemental zinc existed, and performed this secondary analysis to examine which sociodemographic and clinical risk factors were associated with vomiting in children with acute diarrhea. Identifying these factors might help providers and caregivers to stratify the risk for the development of vomiting (and therefore, the associated risks of inadequate oral intake, dehydration, and/or lower adherence to zinc supplementation) during diarrheal illness.

Methods:

We performed a secondary data analysis of 4500 children aged 6-59 months with an acute episode of diarrhea who had been enrolled in a two-center randomized, double blind controlled trial in India and Tanzania. The study sites were peri-urban areas of Delhi and Dar es Salaam, respectively. The trial's protocol and main results have been published^{17,18}. Children with diarrheal illness who presented to outpatient health facilities in India and Tanzania were screened and enrolled by the trial team, with selection meant to approximate a general pediatric population presenting with diarrhea to an ambulatory care setting.

Children aged 6 to 59 months having diarrhea (defined as three or more loose or watery stools in the past 24 hrs) for less than 72 hrs, or dysentery (defined as diarrhea with visible

blood) were included in the study. Participants were also required to have caregivers provide written informed consent and have a high likelihood of staying nearby the study area for the duration of the study. Children with severe acute malnutrition, severe dehydration, or other signs of severe or clinically unstable illness were excluded from the study, as were individuals who had previously enrolled in the trial, were actively enrolled in another clinical trial or who had used zinc supplements in the 72-hour period prior to enrollment¹⁷.

Data collection:

All participants received standard of medical care throughout the trial and were followed for 14 days of zinc administration. Blood specimens for plasma zinc were collected twice throughout the study. Symptoms (diarrhea, vomiting, fever, cough, etc.) and anthropometric data (weight, height, weight-for-length/height) were measured throughout the 60-day study period.

Several clinical and sociodemographic variables were extracted from the trial's dataset for use in this analysis. Clinical factors included child age, prior receipt of rotavirus vaccine, dehydration status, axillary temperature, respiratory rate, presence of intercurrent illness, breastfeeding status, and plasma zinc concentration. (The parent trial was designed to only obtain blood for zinc measurement in ~1/3rd of subjects.) Sociodemographic factors included family socioeconomic status, maternal education, household water quality, household sanitation quality, study site, and child sex.

The trial received ethical approval 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, India¹⁷. Caretakers of all enrolled children signed written informed consent forms.

Outcome variables:

The primary outcome for this analysis was the n (%) of participants with vomiting (at any point) throughout the study period. Vomiting was defined as the forceful expulsion of stomach contents, as opposed to gastro-esophageal reflux, or “spitting up” which was defined as effortless regurgitation. Secondly, vomiting was considered as zinc-related when it was noted within 30 minutes of supplement administration and as non-zinc-related when it occurred more than 30 minutes after supplement administration. Caregiver report via daily written diary provided all reports of vomiting (both zinc-related and non-zinc-related) occurrences except for day 1 zinc-related vomiting, which was measured by direct observation¹⁷.

Statistical analysis:

Baseline subject characteristics were summarized using means and standard deviations (SD) for continuous variables and frequency (percentage) for categorical variables. We used log-binomial models to examine the associations of vomiting at any time, vomiting within 30 minutes and vomiting outside 30 minutes of zinc administration with potential risk factors. Risk ratios and 95% confidence intervals (CIs) were used to assess the associations. Risk factors with P value <0.05 in univariable analyses were entered into multivariable analysis. Covariates considered in the analysis included both sociodemographic (e.g. maternal age, maternal education, age, sex, etc.) and clinical (e.g. prior receipt of rotavirus vaccination, duration of diarrhea before study enrollment, presence of dehydration, dysentery, fever, or tachypnea; prior use of antibiotics, etc.) categories. Two-tailed p-values <0.05 were considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results:

The cohort was divided evenly by study site (n=2250 each) and by intervention arm (5 mg, 10 mg, and 20 mg) groups (Table 1). The mean (SD) age of participants at the time of randomization was 23 (14.9) months with a roughly even distribution by sex (47.9% female). The mothers of study participants were in their late 20s on average with 7 years being the average length of maternal education (Table 1). The most frequent duration of diarrhea was between 24 and 48 hours (82.5%), with an average of 6 stools in the 24h hours preceding enrollment (Table 1). In the Tanzanian cohort 2235 (99.3%) were vaccinated against rotavirus, whereas only 3/2250 (0.001%) of the Indian children were vaccinated (Table 1). The average plasma zinc concentration at enrollment was 73.5 µg/dl for the 29.1% of participants who had this information recorded. Out of that group, 37.6% had a plasma zinc concentration <65 µg/dl at enrollment.

Of the 4500 children enrolled, 26.7% (n=1208) were noted to have vomiting at any point during the trial; 16.2% (n=728) had zinc-related vomiting (within 30 minutes of zinc administration) and 23.2% (n=1037) had vomiting outside the 30-minute time period. The proportion of participants reporting any vomiting was 11.3% on the first day (6.5% reported as zinc-related) (Supplemental Figure 1). Vomiting became less common as the day of illness progressed, with a 50% decline in proportion of vomiting by day 3 (5.7% had any vomiting and 3.0% had zinc-related vomiting) and 75% decline by day 7. Generally, rates of vomiting underwent the highest rates of decline in the first five days, with slow resolution across the rest of the 14-day study.

The univariate analysis for the occurrence of any vomiting during the study period revealed that longer duration of diarrhea before enrollment (>48 hours), dehydration, fever (>38°C), tachypnea (>40 breaths/minute), previous use of antibiotic agent, prior receipt of the rotavirus vaccine, household wealth index above the median, and breastfeeding before enrollment were all associated with higher relative risk of developing any vomiting (Table 2). The 5 mg and 10 mg intervention arms were associated with a lower risk of vomiting, as was older age (12-24 months and 24-60 months compared to 6-12 months), being underweight at enrollment and being stunted at enrollment.

After adjusting for multiple clinical and sociodemographic characteristics and treatment arm, presence of dehydration (RR 1.45, CI 1.10 – 1.92), being underweight at enrollment (RR 1.22, CI 1.05 – 1.41), prior receipt of the rotavirus vaccination (RR 1.89, CI 1.69 – 2.12), and household wealth above the median (RR 1.17, CI 1.07 – 1.29) were associated with a higher relative risk of developing any vomiting throughout the duration of the study period (Table 2). Older age (12-24 months RR 0.83, CI 0.74 – 0.93; 24-60 months, RR 0.50, CI 0.42 – 0.60), and lower zinc dosing (5 mg intervention arm RR 0.73, CI 0.65 – 0.82; 10 mg intervention arm RR 0.84, CI 0.75 – 0.93) were associated with a lower relative risk of vomiting.

Comparing zinc-related and non-zinc-related vomiting (whether or not the vomiting occurred within 30 minutes of zinc administration), there were several shared risk factors associated with a higher risk of any vomiting (presence of dehydration, being underweight, previous use of an antibiotic agent, prior receipt of the rotavirus vaccination, randomization arm) and a lower risk of vomiting (older age) (Tables 3 and 4). In none of these analyses was improved water or sanitation markers associated with a higher risk of vomiting.

Discussion:

In this secondary analysis of a large, multicenter clinical trial of children with acute diarrheal illness receiving zinc supplementation, vomiting affected more than a quarter of children after enrollment, and gradually declined over the course of the 14-day follow-up. Multiple clinical (prior receipt of rotavirus vaccination, underweight status, presence of dehydration) and sociodemographic (younger age, household wealth) risk factors were associated with higher relative risk of vomiting. Of note, when stratified by zinc-related and non-zinc-related vomiting, the study demonstrated only prior use of an antibiotic agent as an additional risk factor associated with increased risk of vomiting in the zinc-related vomiting cohort.

Prior studies aiming to identify risk factors for vomiting in diarrheal illness have been sparse. Most studies identifying risk factors for the development of vomiting have focused on post-operative or chemotherapy-associated vomiting^{19,20}, with few papers examining the relationship between various risk factors and the development of vomiting within the context of acute diarrhea. Several studies examined risk factors associated with the severity of diarrheal illness²¹⁻²³, however, the isolated impact of those risk factors on vomiting has not been clearly defined. A large cohort study of children presenting with vomiting in the absence of diarrhea demonstrated that only 54.6% of cases identified a pathogenic microbial agent²⁴, with the majority of those with an identified pathogen being viral (51.7% of cases). However, no association was made between additional risk factors (other than microbial agent) and the development of vomiting in those illness episodes²⁴.

Of note, one study conducted in Ethiopia demonstrated that vomiting was associated with the withholding of fluid by caretakers within the context of pediatric diarrheal illness²⁵.

However, other risk factors were not identified. The withholding of fluids may be associated with dehydration, which correlates with our finding of dehydration as a significant risk factor for the occurrence of vomiting, although the causal nature of that relationship is unknown.

Zinc supplementation has been noted to be a risk factor for the development of vomiting in diarrheal illness^{13,14,26}, especially in high doses. This has likely resulted in lower treatment adherence rates, as the side effect of vomiting potentially counters the benefit of improved diarrheal symptoms and may act as a disincentive for caretakers to provide an intervention that causes vomiting. The findings of the Zinc Therapeutic Dosing Trial¹⁷ that lower dose zinc was non-inferior to standard dose but safer (i.e., lower risk of vomiting) is likely to change global recommendations for zinc dosing in diarrhea²⁷. This is helpful to consider, alongside the finding in this study that prior use of antibiotics was associated with increased likelihood of vomiting. This could represent a generalized aversion of medications by some children (resulting in vomiting)²⁸, or could be specific to the antibiotics used in diarrheal illness (such as metronidazole), some of which are known to cause side effects of nausea and vomiting²⁹.

This analysis also demonstrates that vomiting appeared to be more prevalent in the first 3-5 days of diarrheal illness, with a sharp reduction in the proportion of study participants reporting vomiting noted from day one compared to day six. These findings could have implications for the recommendations for zinc supplementation dosing during diarrheal illness, as well as for the counseling of families administering nutritional interventions for children with diarrheal illness. Given the lower prevalence of vomiting after five days observed in this large cohort, this time course can be used to describe the natural history of vomiting (both within and outside of the context of zinc supplementation) within diarrheal illness for expectation-setting with caregivers.

Limitations from this study include the difficulty of clearly distinguishing between zinc-related and non-zinc-related causes of vomiting. The study used a cutoff of 30 minutes after zinc administration as the distinction between zinc-related and non-zinc-related vomiting. However, since one pharmacokinetic study of oral zinc administration suggests peak plasma concentration at 2 hours³⁰, the 30-minute time frame may have underestimated the prevalence of zinc-related vomiting. The study also did not quantify the volume of gastric fluid loss via vomiting, which may have led to variation in the classification of an event as vomiting because different caregivers may have different definitions of vomiting (e.g. large volume vomiting episode versus “spit-up” versus vomiting immediately after medication administration). Further, although the sociodemographic risk factors in this study help elucidate potential health-related social needs associated with increased risk of vomiting, the risk factors were not comprehensive. Additional health-related social needs, such as health care access and quality (insurance status, distance from nearest health center, etc.), and social and community context could elucidate further factors altering the risk for development of vomiting. Lastly, data surrounding the enteropathogen causing diarrheal illness were not collected in this study, which could have augmented the understanding of different risk factors for vomiting. The differential exposure to rotavirus vaccine between the two sites may well have altered the enteropathogens associated with illness in the cohort^{24,31}. Since rotavirus vaccine receipt was strongly correlated with study site, the former can be considered as a proxy for the latter. The near 100% concordance of the variables did not allow us to run multivariable models in which both variables were included due to lack of convergence. As a result, although we can speculate that rotavirus vaccination receipt differences between study sites was responsible for the differences in occurrence of vomiting

between the two sites, we cannot isolate the effect of vaccination status from that of study site in our current analysis.

In summary, younger, smaller, dehydrated infants are at higher risk of vomiting during episodes of diarrhea treated with zinc supplementation. Since vomiting is also a risk factor for dehydration, identifying children at higher risk of vomiting in the setting of zinc supplementation can help clinicians determine which children are at highest risk of dehydration and/or inadequate intake and provide appropriate caregiver guidance and counseling. These findings could also promote cost-effective use of urgent and emergent care settings by improving the triaging ability for primary care clinicians counseling families on the decision whether to report for care in those settings. Further research on the enteropathogen causing diarrheal illness and associated vomiting in children might improve the quality of evidence around this common problem.

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Table 1. Baseline Characteristics of 4500 Children with Diarrhea Enrolled in a Clinical Trial of Zinc Supplementation.

	n (%) or mean [SD]
Enrollment country	
- India	2250 (50.0)
- Tanzania	2250 (50.0)
Zinc intervention arms	
- 5 mg	1504 (33.4)
- 10 mg	1498 (33.3)
- 20 mg	1498 (33.3)
Mother's age, years	26.8 [5.0]
Mother's Education, years	7.2 [4.1]
Maternal education >7 years	1990 (44.8)
Household wealth above median	2270 (50.5)
Child age in months at randomization	23.0 [14.9]
Age group at randomization	
- 6 to <12 mo	1256 (27.9)
- 12 to <24 mo	1477 (32.8)
- 24 to <60 mo	1767 (39.3)
Child female sex	2155 (47.9)
Breastfeeding on day before enrollment	2586 (57.6)
Rotavirus vaccination	2238 (49.8)
Duration of diarrhea before enrollment	
- ≤ 24 hr	165 (3.7)
- 25 to 48 hr	3714 (82.5)
- 49 to <72 hr	621 (13.8)
Number of loose or watery stools the child passed in previous 24 hours	5.7 [2.1]
Dysentery	167 (3.7)
Some dehydration	56 (1.2)
Axillary temperature >38°C	122 (2.7)
Observed respiratory rate >40 breaths/min	255 (5.7)

	n (%) or mean [SD]
Cough or difficulty breathing	1267 (28.2)
Vomiting everything at enrollment	3 (0.1)
Ear pain at enrollment	23 (0.5)
Previous use of antibiotic agent	96 (2.1)
Weight-for-age z-score (WAZ)	-1.2 [1.1]
Length/height-for-age z-score (HAZ)	-1.3 [1.2]
Weight-for-length/height z-score (WLZ)	-0.7 [1.0]
Mid-upper-arm circumference for age z score	-0.8 [1.0]
Underweight at enrollment (WAZ < -2)	1034 (23.0)
Stunted at enrolment (HAZ < -2)	1188 (26.4)
Wasted at enrolment (WLZ < -2)	407 (9.0)
Improved water [#]	4455 (99.2)
Improved sanitation ^{\$}	4463 (99.4)
Plasma zinc concentration at enrollment, µg/dl	73.5 [24.9]
Plasma zinc concentration at enrollment <65 µg/dl	492 (37.6)

Values of polytomous variables may not sum to 100% due to rounding.

[#] 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)

Table 2. Risk factors of any vomiting during study period (n=4500)

Variables	n/N (%)	Univariate		Multivariate	
		Risk Ratio	P value	Risk Ratio	P value
Rotavirus vaccination received					
No	397/2259 (17.6%)	Ref.		Ref.	
Yes	806/2238 (36.0%)	2.05 (1.85, 2.28)	<0.001	1.89 (1.69, 2.12)	<0.001
Maternal age >25 years					
No	576/2114 (27.3%)	Ref.			
Yes	623/2346 (26.6%)	0.97 (0.88, 1.07)	0.60		
Maternal education >7 years					
No	668/2455 (27.2%)	Ref.			
Yes	525/1990 (26.4%)	0.97 (0.88, 1.07)	0.54		
Child age, months					
6 to <12	461/1256 (36.7%)	Ref.		Ref.	
12 to <24	457/1477 (30.9%)	0.84 (0.76, 0.94)	0.002	0.83 (0.74, 0.93)	0.001
24 to <60	285/1767 (16.1%)	0.44 (0.39, 0.50)	<0.001	0.50 (0.42, 0.60)	<0.001
Child sex					
Female	566/2155 (26.3%)	Ref.			
Male	637/2345 (27.2%)	1.03 (0.94, 1.14)	0.50		
Household wealth index above median					
No	544/2221 (24.5%)	Ref.		Ref.	
Yes	659/2270 (29.0%)	1.19 (1.08, 1.31)	0.001	1.17 (1.07, 1.29)	<0.001
Breastfeeding before enrollment					
No	382/1904 (20.1%)	Ref.			
Yes	820/2586 (31.7%)	1.58 (1.42, 1.76)	<0.001	1.05 (0.92, 1.20)	0.48
Duration of diarrhea before enrollment					
<=24 hours	40/165 (24.2%)	Ref.		Ref.	
25 to 48 hours	962/3714 (25.9%)	1.07 (0.81, 1.41)	0.64	1.01 (0.77, 1.32)	0.93
49 to <72 hours	201/621 (32.4%)	1.34 (1.00, 1.79)	0.05	0.93 (0.70, 1.25)	0.63
Dysentery					
No	1151/4330 (26.6%)	Ref.			
Yes	51/167 (30.5%)	1.15 (0.91, 1.45)	0.25		
Dehydration					
No	1178/4444 (26.5%)	Ref.		Ref.	
Yes	25/56 (44.6%)	1.68 (1.25, 2.26)	<0.001	1.45 (1.10, 1.92)	0.01
Axillary temperature >38°C					
No	1159/4378 (26.5%)	Ref.		Ref.	
Yes	44/122 (36.1%)	1.36 (1.07, 1.73)	0.01	1.20 (0.94, 1.53)	0.15
Observed respiratory rate >40 breaths/min					
No	1102/4242 (26.0%)	Ref.		Ref.	

Variables	n/N (%)	Univariate		Multivariate	
		Risk Ratio	P value	Risk Ratio	P value
Yes	101/255 (39.6%)	1.52 (1.30, 1.79)	<0.001	0.90 (0.76, 1.07)	0.24
Cough or difficulty breathing					
No	883/3233 (27.3%)	Ref.			
Yes	320/1267 (25.3%)	0.92 (0.83, 1.03)	0.16		
Previous use of antibiotic agent					
No	1163/4395 (26.5%)	Ref.		Ref.	
Yes	40/96 (41.7%)	1.57 (1.24, 2.01)	<0.001	1.20 (0.95, 1.51)	0.12
Plasma zinc concentration at enrollment < 65µg/dl					
No	189/817 (23.1%)	Ref.			
Yes	136/492 (27.6%)	1.19 (0.99, 1.44)	0.07		
Intervention arms					
5 mg	344/1504 (22.9%)	0.73 (0.65, 0.82)	<0.001	0.73 (0.65, 0.82)	<0.001
10 mg	390/1498 (26.0%)	0.83 (0.74, 0.93)	0.002	0.84 (0.75, 0.93)	0.001
20 mg	469/1498 (31.3%)	Ref.			
Underweight at enrollment					
No	952/3466 (27.5%)	Ref.		Ref.	
Yes	251/1034 (24.3%)	0.88 (0.78, 1.00)	0.04	1.22 (1.05, 1.41)	0.008
Stunted at enrollment					
No	942/3311 (28.5%)	Ref.		Ref.	
Yes	260/1188 (21.9%)	0.77 (0.68, 0.87)	<0.001	0.94 (0.81, 1.09)	0.43
Wasting at enrollment					
No	1098/4093 (26.8%)	Ref.			
Yes	105/407 (25.8%)	0.96 (0.81, 1.14)	0.66		
Improved water					
No	12/36 (33.3%)	Ref.			
Yes	1191/4455 (26.7%)	0.80 (0.50, 1.28)	0.35		
Improved sanitation					
No	8/28 (28.6%)	Ref.			
Yes	1195/4463 (26.8%)	0.94 (0.52, 1.69)	0.83		

Risk factors associated with any vomiting (zinc- or non-zinc-related) throughout the study period, with all variables/factors included in univariate analysis and only variables with $p < 0.05$ included in the multivariate analysis.

Table 3. Risk factors of zinc-related vomiting (within 30 min after zinc administration) during study period (n=4500)

Variables	n/N (%)	Univariate		Multivariate	
		Risk Ratio	P value	Risk Ratio	P value
Rotavirus vaccination received					
No	182/2256 (8.1%)	Ref.		Ref.	
Yes	546/2238 (24.4%)	3.03 (2.59, 3.54)	<0.001	2.72 (1.35, 5.47)	0.005
Maternal age >25 years					
No	334/2114 (15.8%)	Ref.			
Yes	392/2346 (16.7%)	1.06 (0.93, 1.21)	0.41		
Maternal education >7 years					
No	415/2455 (16.9%)	Ref.			
Yes	306/1990 (15.4%)	0.91 (0.79, 1.04)	0.17		
Child age, months					
6 to <12	305/1256 (24.3%)	Ref.		Ref.	
12 to <24	272/1477 (18.4%)	0.76 (0.66, 0.88)	<0.001	0.75 (0.64, 0.87)	<0.001
24 to <60	151/1767 (8.6%)	0.35 (0.29, 0.42)	<0.001	0.49 (0.38, 0.62)	<0.001
Child sex					
Female	353/2155 (16.4%)	Ref.			
Male	375/2345 (16.0%)	0.98 (0.85, 1.12)	0.72		
Household wealth index above median					
No	337/2221 (15.2%)	Ref.			
Yes	391/2270 (17.2%)	1.14 (0.99, 1.30)	0.07		
Breastfeeding before enrollment					
No	202/1904 (10.6%)	Ref.		Ref.	
Yes	525/2586 (20.3%)	1.91 (1.65, 2.23)	<0.001	1.23 (1.02, 1.50)	0.03
Duration of diarrhea before enrollment					
<=24 hours	20/165 (12.1%)	Ref.		Ref.	
25 to 48 hours	571/3714 (15.4%)	1.27 (0.84, 1.93)	0.26	1.19 (0.78, 1.81)	0.41
49 to <72 hours	137/621 (22.1%)	1.82 (1.18, 2.82)	0.007	1.12 (0.72, 1.74)	0.62
Dysentery					
No	695/4330 (16.1%)	Ref.			
Yes	33/167 (19.8%)	1.23 (0.90, 1.68)	0.19		
Dehydration					
No	712/4444 (16.0%)	Ref.		Ref.	
Yes	16/56 (28.6%)	1.78 (1.17, 2.71)	0.007	1.42 (0.94, 2.16)	0.10
Axillary temperature >38°C					
No	702/4378 (16.0%)	Ref.			
Yes	26/122 (21.3%)	1.33 (0.94, 1.88)	0.11		
Observed respiratory rate >40 breaths/min					
No	660/4242 (15.6%)	Ref.		Ref.	

Variables	n/N (%)	Univariate		Multivariate	
		Risk Ratio	P value	Risk Ratio	P value
Yes	68/255 (26.7%)	1.71 (1.38, 2.13)	<0.001	0.84 (0.67, 1.05)	0.13
Cough or difficulty breathing					
No	549/3233 (17.0%)	Ref.		Ref.	
Yes	179/1267 (14.1%)	0.83 (0.71, 0.97)	0.02	1.06 (0.91, 1.23)	0.48
Previous use of antibiotic agent					
No	698/4395 (15.9%)	Ref.		Ref.	
Yes	30/96 (31.3%)	1.97 (1.45, 2.67)	<0.001	1.42 (1.06, 1.91)	0.02
Plasma zinc concentration at enrollment < 65µg/dl					
No	99/817 (12.1%)	Ref.		Ref.	
Yes	81/492 (16.5%)	1.36 (1.04, 1.78)	0.03	0.94 (0.72, 1.23)	0.64
Intervention arms					
5 mg	206/1504 (13.7%)	0.71 (0.60, 0.84)	<0.001	0.71 (0.61, 0.83)	<0.001
10 mg	233/1498 (15.6%)	0.81 (0.69, 0.94)	0.007	0.81 (0.69, 0.94)	0.007
20 mg	289/1498 (19.3%)	Ref.			
Underweight at enrollment					
No	598/3466 (17.3%)	Ref.		Ref.	
Yes	130/1034 (12.6%)	0.73 (0.61, 0.87)	<0.001	1.06 (0.85, 1.33)	0.58
Stunted at enrollment					
No	582/3311 (17.6%)	Ref.		Ref.	
Yes	146/1188 (12.3%)	0.70 (0.59, 0.83)	<0.001	1.04 (0.84, 1.29)	0.75
Wasting at enrollment					
No	669/4093 (16.3%)	Ref.			
Yes	59/407 (14.5%)	0.89 (0.69, 1.13)	0.34		
Improved water					
No	9/36 (25.0%)	Ref.			
Yes	719/4455 (16.1%)	0.65 (0.37, 1.14)	0.13		
Improved sanitation					
No	5/28 (17.9%)	Ref.			
Yes	723/4463 (16.2%)	0.91 (0.41, 2.01)	0.81		

Risk factors associated with zinc-related vomiting (within 30 minutes of zinc administration) throughout the study period, with all variables/factors included in univariate analysis and only variables with $p < 0.05$ included in the multivariate analysis.

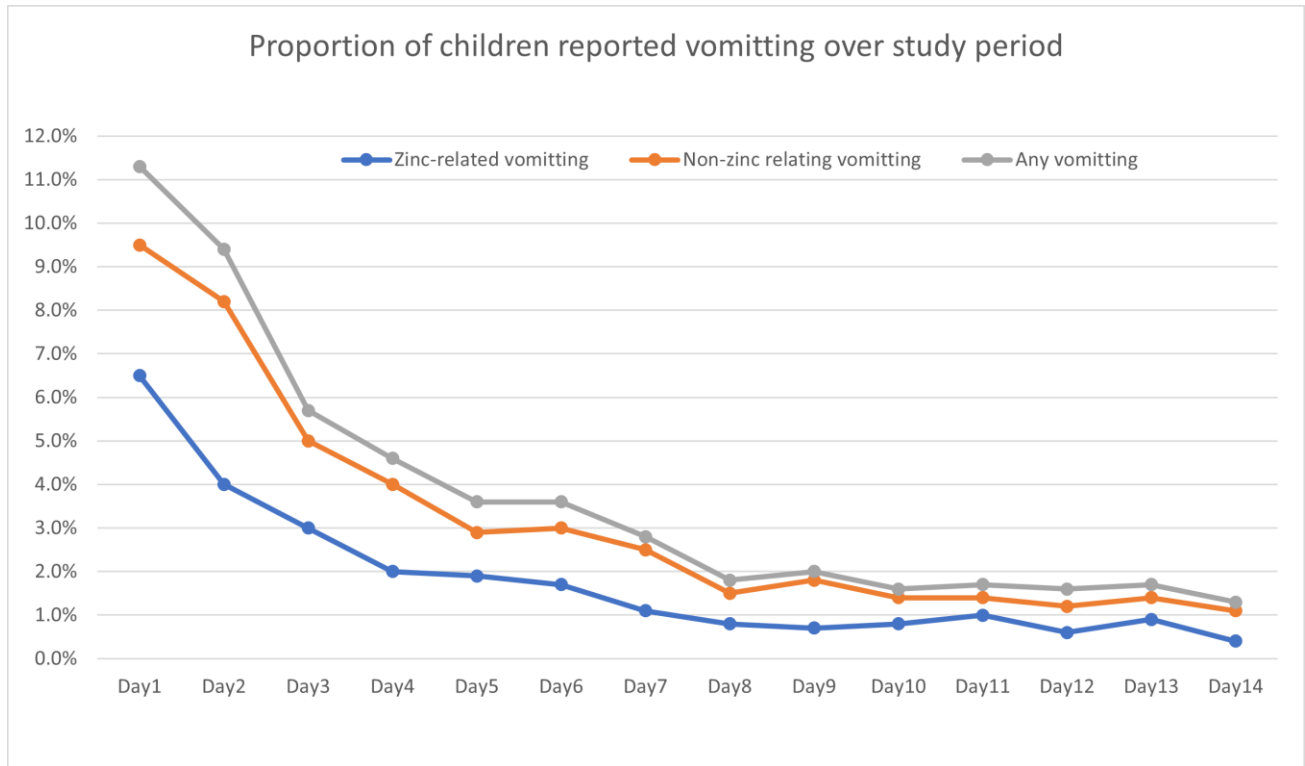
Table 4. Risk factors of non-zinc related vomiting (>30 min after zinc administration) during study period (n=4474)

Variables	Univariate		Multivariate	
	Risk Ratio	P value	Risk Ratio	P value
Rotavirus vaccination received				
No	300/2243 (13.4%)	Ref.	Ref.	
Yes	737/2228 (33.1%)	2.47 (2.19, 2.79)	1.58 (0.58, 4.30)	0.38
Maternal age >25 years				
No	485/2104 (23.1%)	Ref.		
Yes	548/2338 (23.4%)	1.02 (0.91, 1.13)		0.76
Maternal education >7 years				
No	588/2445 (24.1%)	Ref.		
Yes	439/1982 (22.2%)	0.92 (0.83, 1.03)		0.14
Child age, months				
6 to <12	399/1247 (32.0%)	Ref.	Ref.	
12 to <24	396/1470 (26.9%)	0.84 (0.75, 0.95)	0.83 (0.74, 0.94)	0.004
24 to <60	242/1757 (13.8%)	0.43 (0.37, 0.50)	0.54 (0.45, 0.65)	<0.001
Child sex				
Female	484/2140 (22.6%)	Ref.		
Male	553/2334 (23.7%)	1.05 (0.94, 1.17)		0.39
Household wealth index above median				
No	470/2212 (21.3%)	Ref.	Ref.	
Yes	567/2261 (25.1%)	1.18 (1.06, 1.31)	1.17 (1.06, 1.30)	0.002
Breastfeeding before enrollment*				
No	331/1897 (17.5%)	Ref.	Ref.	
Yes	706/2575 (27.4%)	1.57 (1.40, 1.77)	1.06 (0.92, 1.23)	0.40
Duration of diarrhea before enrollment				
<=24 hours	33/164 (20.1%)	Ref.	Ref.	
25 to 48 hours	827/3694 (22.4%)	1.11 (0.82, 1.52)	1.03 (0.77, 1.38)	0.86
49 to <72 hours	177/616 (28.7%)	1.43 (1.03, 1.98)	0.89 (0.65, 1.22)	0.48
Dysentery				
No	994/4305 (23.1%)	Ref.		
Yes	42/166 (25.3%)	1.10 (0.84, 1.43)		0.50
Dehydration				
No	1016/4420 (23.0%)	Ref.	Ref.	
Yes	21/54 (38.9%)	1.69 (1.21, 2.37)	1.39 (1.01, 1.92)	0.04
Axillary temperature >38°C				
No	998/4352 (22.9%)	Ref.	Ref.	
Yes	39/122 (32.0%)	1.39 (1.07, 1.82)	1.07 (0.84, 1.37)	0.60
Observed respiratory rate >40 breaths/min				
No	941/4219 (22.3%)	Ref.	Ref.	
Yes	96/252 (38.10%)	1.71 (1.45, 2.02)	0.96 (0.80, 1.14)	0.63

Variables	Univariate		Multivariate	
	Risk Ratio	P value	Risk Ratio	P value
Cough or difficulty breathing				
No	774/3216 (24.1%)	Ref.	Ref.	
Yes	263/1258 (20.9%)	0.87 (0.77, 0.98)	1.07 (0.95, 1.20)	0.28
Previous use of antibiotic agent				
No	1000/4378 (22.8%)	Ref.	Ref.	
Yes	37/95 (39.0%)	1.71 (1.32, 2.21)	1.28 (1.00, 1.64)	0.048
Plasma zinc concentration at enrollment < 65µg/dl				
No	164/811 (20.2%)	Ref.	Ref.	
Yes	122/492 (24.8%)	1.23 (1.00, 1.51)	0.91 (0.75, 1.11)	0.35
Intervention arms				
5 mg	301/1496 (20.1%)	0.74 (0.65, 0.85)	0.75 (0.67, 0.85)	<0.001
10 mg	333/1488 (22.4%)	0.83 (0.73, 0.94)	0.84 (0.74, 0.94)	0.003
20 mg	403/1490 (27.1%)	Ref.		
Underweight at enrollment				
No	823/3447 (23.9%)	Ref.	Ref.	
Yes	214/1027 (20.8%)	0.87 (0.76, 1.00)	1.28 (1.10, 1.48)	0.001
Stunted at enrollment				
No	826/3292 (25.1%)	Ref.	Ref.	
Yes	210/1181 (17.8%)	0.71 (0.62, 0.81)	0.89 (0.76, 1.04)	0.13
Wasting at enrollment				
No	947/4068 (23.3%)	Ref.		
Yes	90/406 (22.2%)	0.95 (0.79, 1.15)		0.61
Improved water				
No	11/36 (30.6%)	Ref.		
Yes	1026/4437 (23.1%)	0.76 (0.46, 1.24)		0.27
Improved sanitation				
No	8/28 (28.6%)	Ref.		
Yes	1029/4445 (23.2%)	0.81 (0.45, 1.46)		0.48

Risk factors associated with any non-zinc-related vomiting (vomiting occurred more than 30 minutes after zinc administration) throughout the study period, with all variables/factors included in univariate analysis and only variables with $p < 0.05$ included in the multivariate analysis.

Supplemental Figure 1:



Proportion of children who reported vomiting (all vomiting, zinc-related and non-zinc-related) by day throughout the study period.