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Zinc Supplementation in the Management of Acute Diarrhea in High-Income Countries-A Systematic Evaluation and Meta-Analysis

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Abstract

The World Health Organisation (WHO) and the United Nations International Children's Emergency Fund (UNICEF) recommend zinc supplementation for children with diarrhea. However, Low and Middle-Income Countries (LMICs) conducted the majority of the studies supporting this recommendation. Although the mortality rate of acute diarrhea in developed countries is low, diarrhea leads to a high number of clinical care and hospital admissions, which represents a significant economic burden. This systematic review assessed the therapeutic benefits of zinc supplementation in the treatment of acute diarrhea in children living in high-income countries. We conducted a literature search on the Medline, Embase, Cochrane, and SciELO databases to find published randomised controlled trials on zinc supplementation and acute diarrhea in children residing in developed countries. We conducted a systematic literature search of the databases, uncovered 609 titles, and included 3 trials, totalling 620 treated children with acute diarrhea, after reviewing abstracts and full manuscripts for inclusion and exclusion criteria. Two studies showed that zinc did not interfere with the duration of diarrhea. According to the Cochrane Risk of Bias RoB 2, risk was considered low in two studies and some concerns in another. There was no statistically significant reduction in the mean RR for the occurrence of diarrheal episodes after 7 days of zinc supplement administration (0.4% *vs.* 0.6%; RR 0.73; 95% CI 0.28-1.92; p=0.53; I2=16%). Zinc supplementation did not reduce the duration of acute diarrhea among children living in developed countries.

Keywords: Acute diarrhea; Zinc supplementation; Children; High-income countries

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Introduction

Diarrhea is the third leading cause of death in children 1–59 months of age, most of which occur in developing countries [1]. According to the World Health Organization (WHO), acute diarrhea is defined as the discharge of loose stools or liquid stools ≥ 3 times per day for ≥ 3 days and <14 days [2]. Diarrhea can quickly lead to fluid and electrolyte loss and may be life-threatening, especially in young infants and malnourished children. Besides, diarrhea promotes nutritional deficiencies, reduces immunity, and impairs growth and development [3-5].

Worldwide, zinc deficiency is common, but reports of severe deficiency are rare [6]. Zinc is an important micronutrient for cellular growth, cellular differentiation, and metabolism [7]. Zinc deficiency may limit immunity and impair resistance to infections. Many studies have shown that zinc supplementation may reduce the duration and severity of diarrhea [8-11]. A systematic review of randomised controlled trials found that oral zinc supplementation significantly reduces the duration of diarrhea; however, only one of the 18 included studies took place in a developed country [12]. Another systematic review observed no consistent benefit with zinc trials to treat diarrhea [13]. A Cochrane systematic review suggests that zinc may be of benefit to children aged six months or more in areas where the prevalence of zinc deficiency or malnutrition is high [14].

The World Health Organisation (WHO) and the United Nations International Children's Emergency Fund (UNICEF) recommend zinc supplementation for children with acute diarrhea [15], last

updated on 9 August, 2023. However, few studies were conducted in developed countries, thereby limiting the global World Health Organisation (WHO) recommendations for diarrhea. This systematic review aims to assess the therapeutic benefits of zinc supplementation in the treatment of acute diarrhea in children living in high-income countries.

Materials and Methods

We developed this systematic review with meta-analysis in accordance with the Cochrane handbook for systematic reviews of interventions and reported it using the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist [16]. We registered this study under Prospero (CRD42024516946). Ethical approval is not required for this study, as it is a systematic review.

We conducted a literature search using Medline, Embase, Cochrane, and Scielo electronic databases, without any language restrictions. We selected only Randomised Controlled Trials (RCTs) conducted in developed countries. The search included trials that were published in any language. Two reviewers (Túlio Revoredo and João Guilherme Bezerra Alves) assessed the eligibility of each record. Initially, we screened the title and abstract. At this stage, we excluded studies that were not RCTs, not conducted in developed countries, and did not include data on human subjects, acute diarrhea, or oral zinc administration. We obtained complete articles to conduct further reviews of pertinent studies. A third reviewer (Lucas Victor Alves) resolved any disagreements over the selection of studies.

The following keywords were utilized: "zinc", "zinc supplementation", "oral zinc", "diarrhea", "acute diarrhea", "diarrhea", and "randomised controlled trial", "randomised clinical trial", or "randomised clinical trial". We used a form to extract relevant data from studies, including year, country, study design, population, setting, blinding, allocation concealment, sample size, intervention, and outcomes. Moreover, to conduct our statistical pooling, we solely extracted data from studies' intention-to-treat analyses. Finally, we used the Web Plot Digitizer tool to extract pertinent data from Kaplan-Meier curves and incorporate it into our meta-analysis.

Eligibility criteria

According to the World Bank criteria, this review included RCTs conducted in developed countries, while it excluded studies conducted in Low and Middle-Income Countries (LMIC). We selected studies that only included children with acute diarrhea. The intervention consists of oral zinc administration alone, without any combination. The primary outcome was the duration of diarrhea. Secondary outcomes were stool frequency (measured by the exact number of defecations recorded per day), vomiting duration, hospitalisation and death from diarrhea.

Risk-of-bias assessment

The Risk-of-Bias RoB 2 Toll evaluated the risk of bias of included RCTs based on seven domains:

- The randomization process;
- Deviations from intended intervention;
- Missing outcome data;
- Outcome measurement;
- Selection of the reported results;
- Incomplete reporting; and
- power calculation/sample size.

Before assessment, the reviewers were trained [17]. A third reviewer (Lucas Victor Alves) resolved any disagreements.

Statistical analysis

We compared dichotomous endpoints using Risk Ratios (RR) and 95% confidence intervals. P values ≥ 0.05 were considered significant for the rejection of the null hypothesis that there were no differences in effects between interventions. We adopted the Mantel-Haenszel test for dichotomous data. We used a DerSimonian and Laird random-effects model to incorporate the assumption that true effect sizes varied between studies.

Moreover, to measure and analyse heterogeneity, we utilised the Cochran Q test and I2 statistics. P values ≥ 0.10 were considered significant for the rejection of the null hypothesis that the studies shared a common true effect size. We used the I2 statistic to assess the percentage of variance in observed effect sizes due to heterogeneity. Due to the small number of included studies, we opted not to incorporate prediction intervals to assess heterogeneity or funnel plots to search for publication bias.

We used Cochrane's Review Manager Web for statistical analysis.

Results

Searching the following databases yielded a total of 629 studies: PubMed (305), Embase (214), Cochrane (101), and SciELO [9]. After excluding duplicate manuscripts (303) and studies performed in LMIC countries (322), 4 studies showed potential relevance for the full analysis. We then screened the full texts of the remaining 4 articles for eligibility, excluding one because it did not perform the intervention with only zinc. As a result, this systematic review included three articles [18-20] **(Figure 1)**.

The randomised controlled trial studies included 620 children with acute diarrhea, with sample sizes ranging from 87 to 392. The age of participants ranged from 3 months to <11 years old. **Table 1** displays the characteristics of the included studies.

Valery et al., in Australia, studied 392 Aboriginal children, < 11 years old, with diarrhea supplemented with zinc, vitamin A, or combined zinc and vitamin A. They found no significant effect on the duration of diarrhea; the median diarrhea duration after starting supplementation was 3.0 days for the zinc supplemented and placebo groups (P values of 0.25 and 0.69, respectively).

Patro, et al., in Poland, studied 69 children in the zinc-supplemented group compared with 72 children in the control group, and there was no significant difference in the duration of diarrhea (P >.05). Similarly, they found no significant difference in secondary outcome measures (frequent stool, vomiting, intravenous fluid intake, and the number of children with diarrhea lasting >7 days).

Crisinel et al., in Switzerland, studied 87 children (median age 14 months; range 3.1–58.3); 42 received zinc supplementation

and 45 received placebo. There was no difference in the duration or frequency of diarrhea, but only 5% of the zinc group still had diarrhea at 120 hour of treatment, compared to 20% in the placebo group (P = 0.05). The average length of diarrhea in zinc-treated patients was 47.5 hours (18.3–72 hours), which was significantly longer than the average length of diarrhea in the placebo group (76.3 hours; IQR 52.8–137 hours) (P=0.03). The frequency of diarrhea was also lower in the zinc group (P=0.02). The primary outcome was determined by intention-to-treat analysis, whereas the significant difference in median diarrhea duration was determined by per-protocol analysis.

We have assessed the risk of bias in the included studies. **Table 2** displays the risk of bias in the included studies. We classified two studies as "low risk" [17,18], and one as "moderate risk" due to missing data.

There was no statistically significant reduction in the mean RR in the occurrence of diarrheal episodes after 7 days of zinc supplement administration (0.4% *vs.* 0.6%; RR 0.73; 95% CI 0.28-1.92; p = 0.53; I2 = 16%); The mean RR for comparable studies could fall anywhere between 0.28 and 1.98, as represented by the 95% confidence interval. In regards to heterogeneity, we still can't reject the null hypothesis that all studies share a common true effect size (p=0.30) through the use of Cochrane's Q statistic **(Figure 2, Table 3).**

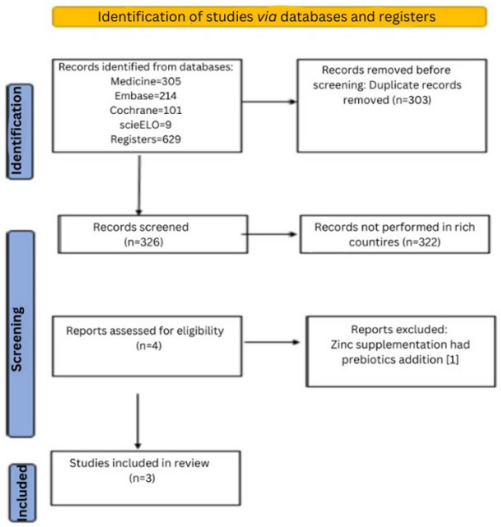

Figure: 1 Flow chart of identification of studies *via* databases and registers.

Table 1: Characteristics of studies included in this systematic review.

Authors and year of publication	Country	Setting	Design	Allocation concealment	Blinding	Sample size	Age (years)	Duration of diarrhea (p)
Valery, et al. 2005 [18]	Australia	Hospital	RCT	Yes	No	392	<11 years	0.69
Patro, et al. (2010) [19]	Poland	Hospital	RCT	Yes	Yes	141	3–48 months	>0.05
Crisinel, et al. (2015) [20]	Switzerland	Hospital	RCT	Yes	No	87	3.1 - 50.3 months	0.03

Table 2: Assessment of the risk of bias based on the Cochrane Risk of Bias 2 checklist. Note: (+) low risk of bias; (?) moderate risk of bias.

Study references	Randomization	Deviations from the intended intervention	Missing outcome data	Outcome Measurements	Selective reporting	Incomplete reporting	Study power calculation/ Sample size justification
Valery, et al. 2005 [18]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Patro, et al. (2010) [19]	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Crisinel, et al. (2015) [20]	(+)	(+)	(?)	(+)	(+)	(+)	(+)

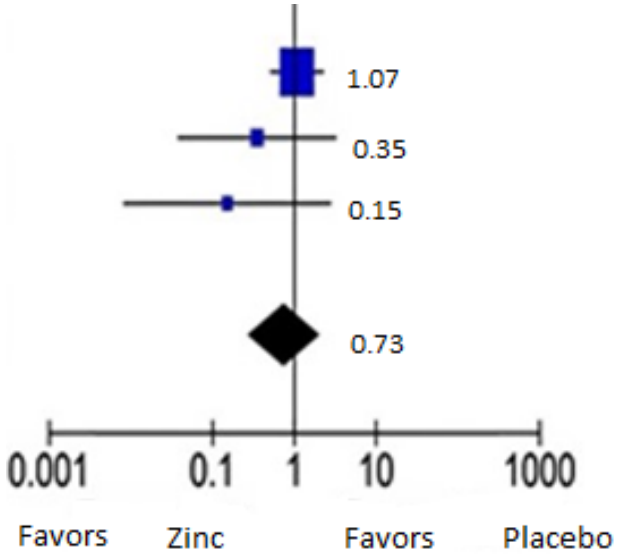

Figure: 2 Forest plot for the occurrence of diarrheal episodes after seven days of zinc supplementation (risk ratio M-H, random, 95% cl).

Table 3: Forest plot for the occurrence of diarrheal episodes after 7 days of zinc supplementation.

	Zinc		Placebo		Risk ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% cl
Valery, et al. 2005 [18]	13	207	12	205	73.8%	1.07 (0.50,2.30)
Patro, 2010 [19]	1	69	3	72	16.3%	0.35 (0.04,3.26)
Crisinel, 2015 [20]	0	37	3	39	10.0%	0.15 (0.01,2.82)
Total (95% cl)		313		316	100.0%	0.73 (0.28,1.92)
Total events	14		18			
Heterogeneity: Tau2=0.18; Chi2 =2.38, df=2 (P=0.30); I2=16%						
Test for overall effect: Z=0.63 (P=0.53)						
Test for subgroup differences: Not applicable						

Discussion

The findings of this systematic review did not suggest the benefits of therapeutic zinc supplementation for diarrhea among children in high-income countries, despite the detection of only three randomised controlled trials. In rich countries, the effects of zinc treatment, which include reductions in episode duration, stool output, stool frequency, and length of hospitalisation, were not the same as in studies performed in low- and middle-income countries. These results suggest that zinc therapy for diarrhea seems not to be beneficial in high-income countries.

Patro, et al., observed no beneficial effect of zinc supplementation on diarrhea duration or severity [18]. They emphasise that they studied well-nourished and healthy children, who were therefore unlikely to be zinc deficient. T The authors attribute their inconsistent results with the majority of previously conducted trials, systematic reviews, and meta-analyses that have demonstrated an anti-diarrheal effect of zinc in children to the fact that these studies took place in countries with a medium or low Human Development Index (HDI), where malnutrition and zinc deficiency are significant issues. They also stated that countries with a high or very high HDI have not conducted any studies evaluating the effects of zinc for the treatment of acute diarrhea.

Valery, et al., came to the conclusion that hospitalised Aboriginal children in Australia may not benefit from zinc supplementation in the management of acute diarrhea [19]. However, they clarify that their findings may not apply to children suffering from malnutrition. They reported that their results for zinc supplementation differ from those in other settings because supplementation is only effective in populations with a low baseline level of these micronutrients. They add that their results suggest that zinc supplementation has a positive effect on stunted children.

This systematic review included only one study that found a difference in the duration of diarrhea: 47.5 hours (18.3–72) in the zinc group and 76.3 hours (52.8–137) in the placebo group (P = 0.03) [20]. However, this study has some limitations. First, they were unable to recruit the expected number of patients based on their calculations. Second, a large number of children were lost to follow-up; 60 patients, out of a total of 148 patients recruited for this study, were lost to follow-up without any available post-baseline data. Third, they had poor compliance, probably due to zinc's metallic taste.

Another study, which was not part of our systematic review, showed that zinc supplementation had a positive effect on acute diarrhea in a population of Italian children aged 3 to 36 months (for a duration less than 24 hours) [21]. However, they used an Oral Rehydration Solution (ORS) containing zinc and probiotics in addition to oral zinc for the intervention. For this reason, the question remains whether the effect was due to zinc or probiotics.

The possible zinc mechanisms of action against diarrhea are not well understood. It may include improved absorption of water and electrolytes by the intestine, better regeneration of the gut epithelium, an increased number of enterocyte brush border enzymes, and an enhanced immune response [22,23]. However, it is questionable whether these actions are independent of zinc deficiency in the host. This systematic review pointed to this.

Many randomised controlled trials performed in LMIC countries have reported that oral zinc supplementation is effective in reducing the duration of acute diarrhea, although some point to divergent results [24-32]. Based on these results, the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) recommend oral zinc supplementation as a universal treatment for all children with acute diarrhea (WHO/UNICEF) [15]. On the other side, according to the recommendations of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases (ESPGHAN/ESPID), there is not enough evidence to support its routine use in children with acute diarrhea living in Europe, where zinc deficiency is rare [33]. Although the mortality rate of acute diarrhea in developed countries is low, diarrhea leads to a high number of clinical care and hospital admissions, which represents a significant economic burden.

Strengths and Limitations

The strength of this study is its pioneering use of synthesised data from randomised clinical trials to evaluate the efficacy of zinc supplementation for the management of acute diarrhea in children living in developed countries. This study also followed all the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [16].

In regards to our meta-analysis, one limitation stems from variations in the defined duration of diarrhea episodes. While Patro et al., provided data solely for the prevalence of episodes lasting more than 7 days, [19] Valery et al., and Crisinel et al., reported data for episodes lasting 7 days or longer [18,20]. Despite this inconsistency, we chose to combine this data for our pooling.

Additional limitations arise from variations in the age inclusion criteria across studies. Patro et al., included children up to a maximum of 4 years old (19), whereas Valery et al., extended their inclusion criteria to children up to 11 years old. Thus, even if we couldn't reject the null hypothesis that heterogeneity wasn't present, this broader range likely does introduce heterogeneity into our meta-analysis [18]. Furthermore, another potential source of heterogeneity arises from the study by Valery et al., as they included data on zinc supplementation among patients also receiving vitamin A supplements, not providing stratified data for patients receiving solely zinc supplementation against patients receiving solely the placebo [18].

Finally, the primary constraint in our meta-analysis is undoubtedly the limited number of studies included. In random-effects meta-analysis, this poses a significant concern as it inhibits the accurate calculation of between-study variance. Consequently, this may lead to unreliable estimates for the summary effect, its associated confidence interval, and the metrics pertaining to heterogeneity. Hence, readers should exercise caution when interpreting our results and consider their limited scope. Nevertheless, despite these acknowledged limitations, conducting a meta-analysis is preferable to relying on an ad-hoc summary of the evidence [34].

Conclusion

Zinc supplementation did not reduce the duration of acute diarrhea among children living in developed countries. This result supports the hypothesis that the anti-diarrheal effect of zinc is dependent on zinc deficiency. The World Health Organisation (WHO) and United Nations International Children's Emergency Fund (UNICEF) recommended regimen of therapeutic zinc should include only low and middle-income countries.

Highlights

New points in the study

- Zinc supplementation did not reduce the duration of acute diarrhea among children living in developed countries.
- The anti-diarrheal effect of zinc is dependent on zinc deficiency.
- The WHO and UNICEF recommended regimen of therapeutic zinc should not include high-income countries.

Known points in the study

- Zinc supplementation may reduce the duration and severity of diarrhea in poor countries.
- The World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) recommend zinc supplementation for children with acute diarrhea.

Declarations

Conflict of interest

The authors declare no conflict of interest

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