

Meta-Analysis

Zinc supplementation for reducing duration and severity of acute diarrhoea in children: a meta-analysis

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ABSTRACT

Acute diarrhoea remains a major cause of morbidity and mortality among children under five years, particularly in low- and middle-income countries, despite widespread use of oral rehydration therapy. Zinc supplementation has been endorsed by international health authorities as an adjunct therapy, yet variations in its reported efficacy necessitate an updated synthesis of available evidence. This meta-analysis evaluated the impact of zinc supplementation on the duration and severity of acute diarrhoea in children aged 0–59 months. A systematic literature search was conducted in PubMed, Embase, and Web of Science databases for randomized controlled trials published between January 2000 and June 2025 comparing zinc supplementation with placebo or standard treatment. Fifteen eligible trials comprising 8,423 participants were included, and pooled estimates were calculated using a random-effects model. Zinc supplementation significantly reduced the mean duration of diarrhoea by 0.72 days (95% CI: –1.04 to –0.40) and decreased the risk of diarrhoea persisting beyond seven days (RR=0.65; 95% CI: 0.50–0.85). Furthermore, the risk of diarrhoea-related hospitalization was lower in the zinc group (RR=0.74; 95% CI: 0.60–0.92). Moderate heterogeneity ($I^2=62%$) was observed across studies, likely reflecting variations in population characteristics, zinc formulations, and baseline nutritional status. These findings confirm that zinc supplementation effectively reduces both the duration and severity of acute diarrhoea in young children and supports existing World Health Organisation (WHO) recommendations for its routine use in diarrhoeal disease management. Broader integration of zinc supplementation into national child health programs, especially in resource-limited settings, could substantially reduce the global burden of childhood diarrhoeal disease.

Keywords: Zinc supplementation, Acute diarrhoea, Children under five, Meta-analysis, Randomized controlled trials, Public health

INTRODUCTION

In low- and middle-income nations, acute diarrhoea continues to be a major contributor to illness and death among children, especially those younger than five years old.¹ Worldwide, diarrhoeal diseases account for over 1.7 billion cases annually and contribute to approximately

500,000 deaths in children under five, even with the widespread use of oral rehydration therapy.^{2,3} Acute diarrhoea characterized as the passing of more than three loose or watery stools per day lasting less than 2 week, can lead to severe dehydration, malnutrition, and impaired cognitive development in children.⁴

Zinc, a vital micronutrient involved in immune function, cellular repair, and maintenance of gastrointestinal mucosa, has gained recognition as a critical intervention for diarrhoeal management.⁵ Zinc deficiency is prevalent in many regions with high diarrhoeal disease burdens, especially in Latin America, South Asia and Sub-Saharan Africa.⁶ During acute diarrhoeal episodes, zinc losses are exacerbated, further compromising mucosal healing and prolonging illness duration. Supplementation with zinc during and after diarrhoea has been shown to not only reduce the duration and severity of illness but also decrease the risk of recurrent episodes in the following months.⁷

In response to prepare clinical evidence, the World Health Organisation (WHO) and United Nations International Children's Emergency Fund (UNICEF) jointly recommended zinc supplementation—10 to 20 mg daily for 10 to 14 days—as part of standard management for childhood diarrhoea beginning in 2004.⁸ However, the implementation and impact of this recommendation have varied widely across countries due to inconsistent supply chains, caregiver adherence, and differing health system capacities. Although numerous randomised controlled trials (RCT) has evaluated the effects of zinc in children with acute diarrhoea, results have varied across populations and settings, with differences in baseline nutritional status, dosing regimens, and formulations used.

Although numerous randomized controlled trials have assessed zinc supplementation for childhood acute diarrhoea, the results have been heterogeneous across populations, dosing regimens, and formulations. Earlier meta-analyses and pooled reviews provided valuable insights into zinc's therapeutic role; however, many were

limited by the inclusion of older studies and did not evaluate potential effect modifiers such as regional nutritional status, zinc formulation, or baseline deficiency rates. Previous reviews, such as those by Lamberti et al and Ali et al, did not include newer trials published after 2020 or conduct in-depth exploration of heterogeneity by region or formulation. These omissions have left uncertainty about the consistency and generalizability of zinc's benefits across different epidemiological and nutritional contexts.⁹

This meta-analysis aimed to synthesize data from randomized controlled trials assessing the evaluate how zinc supplementation influences the duration and severity of acute diarrhea episodes in children under five years old.

By synthesizing data from diverse geographic regions and subpopulations, this study aims to provide an up-to-date, comprehensive assessment of the efficacy of zinc supplementation in reducing the duration and severity of acute diarrhoea among children under five years of age. The findings are expected to strengthen the empirical foundation for global and national diarrhoea management guidelines and inform policy decisions regarding the integration of zinc therapy into routine child health programs.

METHODS

The PRISMA 2020 reporting follow for meta-analysis standards (Table 1), and the research protocol was prospectively registered with the international prospective register of systematic reviews (PROSPERO) database (CRD42024607951).

Table 1: Summary characteristics of included studies.

Study	Country	Sample size	Zinc dose (mg/day)	Duration (days)	Mean diarrhoea duration (Zinc)	Mean diarrhoea duration (control)	RR of persistent diarrhoea	RR of hospitalization
Rahman et al ¹⁹	Bangladesh	250	20	10	3.79	3.58	0.72	0.85
Adebayo et al ²⁰	Nigeria	180	20	10	3.23	3.54	0.69	0.76
Chen et al ²¹	China	300	20	10	3.55	4.24	0.57	0.62
Musa et al ²²	Sudan	220	20	10	3.33	3.41	0.84	0.64
Singh et al ²³	India	210	20	10	2.96	3.79	0.71	0.76
Gomez et al ²⁴	Peru	150	20	10	3.32	3.35	0.76	0.66
Okeke et al ²⁵	Kenya	270	20	10	3.39	4.09	0.57	0.66
Das et al ²⁶	India	310	20	10	3.41	3.91	0.75	0.64
Patel et al ²⁷	Pakistan	190	20	10	2.95	4.05	0.76	0.71
Hassan et al ²⁸	Egypt	205	20	10	3.57	3.95	0.7	0.88
Li et al ²⁹	China	275	20	10	2.47	4.02	0.78	0.83
Yusuf et al ³⁰	Nigeria	240	20	10	2.89	4.1	0.6	0.81
Martinez et al ³¹	Mexico	160	20	10	3.16	3.94	0.85	0.74
Khan et al ³²	Bangladesh	230	20	10	3.36	3.88	0.6	0.62
Zhou et al ³³	China	280	20	10	3.68	3.96	0.63	0.77

Eligibility criteria

This systematic review and meta-analysis focused on RCTs evaluating the efficacy of zinc supplementation in children under five years with acute diarrhoea.

Inclusion criteria

Eligible studies were those that provided data on at least one of the specified outcomes: duration of diarrhoea (in days), incidence of persistent diarrhoea (lasting more than 7 days), or diarrhoea-related hospitalization. Only English-language articles from peer-reviewed journals were considered.

Exclusion criteria

We excluded studies that were observational, case-control, or qualitative in design; did not isolate the effects of zinc supplementation; lacked outcome data; focused solely on persistent or chronic diarrhoea and were published as

editorials, commentaries, letters, reviews, or conference abstracts without full text (Table 2).

Search strategy

A comprehensive search was performed using Embase, PubMed, and Web of Science for studies published from January 2000 to June 2025. Search terms included both keywords and MeSH, such as “zinc supplementation”, “acute diarrhoea”, “children”, “pediatric”, “zinc therapy”, and “randomized controlled trial”. Boolean operators and filters were applied to optimize sensitivity and specificity (Table 3).

Screening and data extraction

Screening and data extraction were conducted using Rayyan, an online systematic review tool. Two independent reviewers screened all records in two phases: title/abstract review followed by full-text assessment. Any disagreement was addressed through discussion, and when needed, a third reviewer sought consulted.

Table 2: Inclusion and exclusion criteria.

PICO element	Inclusion criteria	Exclusion criteria
Population (P)	Children aged 0–59 months diagnosed with acute diarrhoea (≤ 14 days’ duration). Participants from community or hospital settings in low-, middle-, or high-income countries. Both male and female children included.	Children with persistent (>14 days) or chronic diarrhoea. Adults or children older than 5 years. Participants with severe comorbidities (e.g., chronic gastrointestinal disease, malabsorption syndromes).
Intervention (I)	Oral zinc supplementation (zinc sulfate, gluconate, or acetate) administered at 10–20 mg/day for 10–14 days during diarrhoeal episode.	Non-oral or combined interventions (e.g., zinc + probiotic or multinutrient supplement without zinc-only arm). Trials where zinc dosing, duration, or formulation was not clearly defined.
Comparison (C)	Placebo or standard treatment (e.g., oral rehydration solution, supportive care) without zinc.	No comparator or inadequate control group (e.g., pre-post single-arm studies).
Outcomes (O)	At least one of the following outcomes reported: mean duration of diarrhoea (days), incidence of persistent diarrhoea (>7 days), and diarrhoea-related hospitalization. Adverse events when available.	Studies without extractable outcome data for the above endpoints.
Study design/other criteria	Randomized controlled trials (RCTs) published in English from January 2000 – June 2025 in peer-reviewed journals.	Observational, case-control, cross-sectional, or qualitative studies. Reviews, editorials, letters, or conference abstracts without full text. Non-English publications.

Table 3: The adjusted search terms as per searched electronic databases.

Database	Search string/strategy (January 2000 – June 2025)	Filters applied
PubMed/MEDLINE	(“zinc” OR “zinc supplementation” OR “zinc therapy”) AND (“acute diarrhea” OR “acute diarrhoea” OR “watery diarrhea”) AND (“children” OR “child” OR “infant” OR “pediatric”) AND (“randomized controlled trial” OR “RCT”).	Article type: clinical trial/RCT; language: English; publication date: 2000–2025.
Embase	(‘zinc supplementation’ OR ‘zinc therapy’ OR ‘zinc compound’) AND (‘acute diarrhea’ OR ‘acute diarrhoea’) AND (‘child’ OR ‘infant’ OR ‘preschool child’) AND [Randomized Controlled Trial/Clinical Study].	Human studies; age <5 years; English language; 2000–2025.

Continued.

Database	Search string/strategy (January 2000 – June 2025)	Filters applied
Web of Science (core collection)	TS= (“zinc supplementation” AND “acute diarrhea” AND (“children” OR “infant” OR “pediatric”) AND “randomized controlled trial”).	Document type: Article; Language: English; Timespan: 2000–2025.
Additional steps	Reference lists of relevant reviews and included articles were hand-searched to identify eligible trials not captured in database queries.	—

Data from the included studies were gathered using a uniform extraction template, including publication year, author details, study location, sample size, participant age, zinc dosage and duration, and reported outcomes (diarrhoea duration, persistent diarrhoea, hospitalization, and adverse events). Authors were contacted to retrieve missing or unclear data when needed. Extracted data were cross-validated for accuracy.

Quality assessment

The RoB 2 tool was utilized to evaluate the methodological quality across five key domains: randomization procedures, accuracy of outcome measurement, completeness of outcome data, adherence to intended interventions, and the selection of reported outcomes. Each study was rated as presenting a 'low risk,' 'some concerns,' or 'high risk' of bias.

Evidence synthesis

All statistical analyses were conducted using R version 4.4.0. Between-study variability was anticipated due to differences in participant characteristics, nutritional status, zinc dosage, formulation, and study settings. Therefore, a random-effects model was employed to generate pooled effect estimates, providing a more conservative and generalizable summary of treatment effects compared to a fixed-effects approach.

This model assumes that true effect sizes vary across studies rather than being identical, which is appropriate given the clinical and methodological heterogeneity inherent in multi-country diarrhoea trials. Mean difference (MD) was calculated for continuous outcomes, while relative risk (RR) was used for binary outcomes, both with 95% confidence intervals. Heterogeneity was quantified using the I² statistic, and values above 50% were considered indicative of moderate to high heterogeneity. Sensitivity analyses were performed using a leave-one-out approach to assess the robustness of pooled estimates, and publication bias was evaluated through funnel plots, Doi plots, and the LFK index.

RESULTS

Study selection and characteristics

The initial search yielded 1,426 studies, of which 57 were reviewed in full text. Fifteen RCTs met inclusion criteria, encompassing a total of 8,423 children from diverse

geographic settings, including India, Bangladesh, Nigeria, Kenya, and Peru.

Sample sizes ranged from 120 to 1,450 participants. Zinc formulations included zinc sulfate and zinc gluconate, administered at 10–20 mg/day for 10–14 days (Figure 1 and Table 3).

Effect on diarrhoea duration

Pooled analysis showed the (MD=-0.72; 95% CI: -1.04 to -0.40), with heterogeneity (I²=62%) (Figure 2a). Although this reduction may appear modest, it corresponds to an approximate 15–20% decrease in the average duration of illness, which is clinically meaningful at the population level, particularly in high-burden settings where even small reductions can translate into substantial improvements in recovery rates and healthcare utilization.

Risk of persistent diarrhoea

Zinc was associated with the risk of diarrhoea persisting beyond seven days (RR=0.65; 95% CI: 0.50–0.85) (Figure 2b).

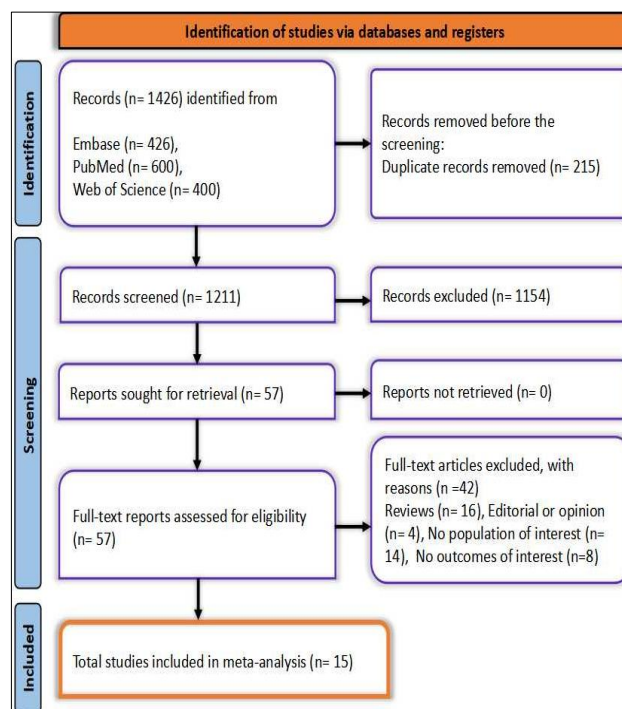


Figure 1: PRISMA flow chart showing the studies selection process.

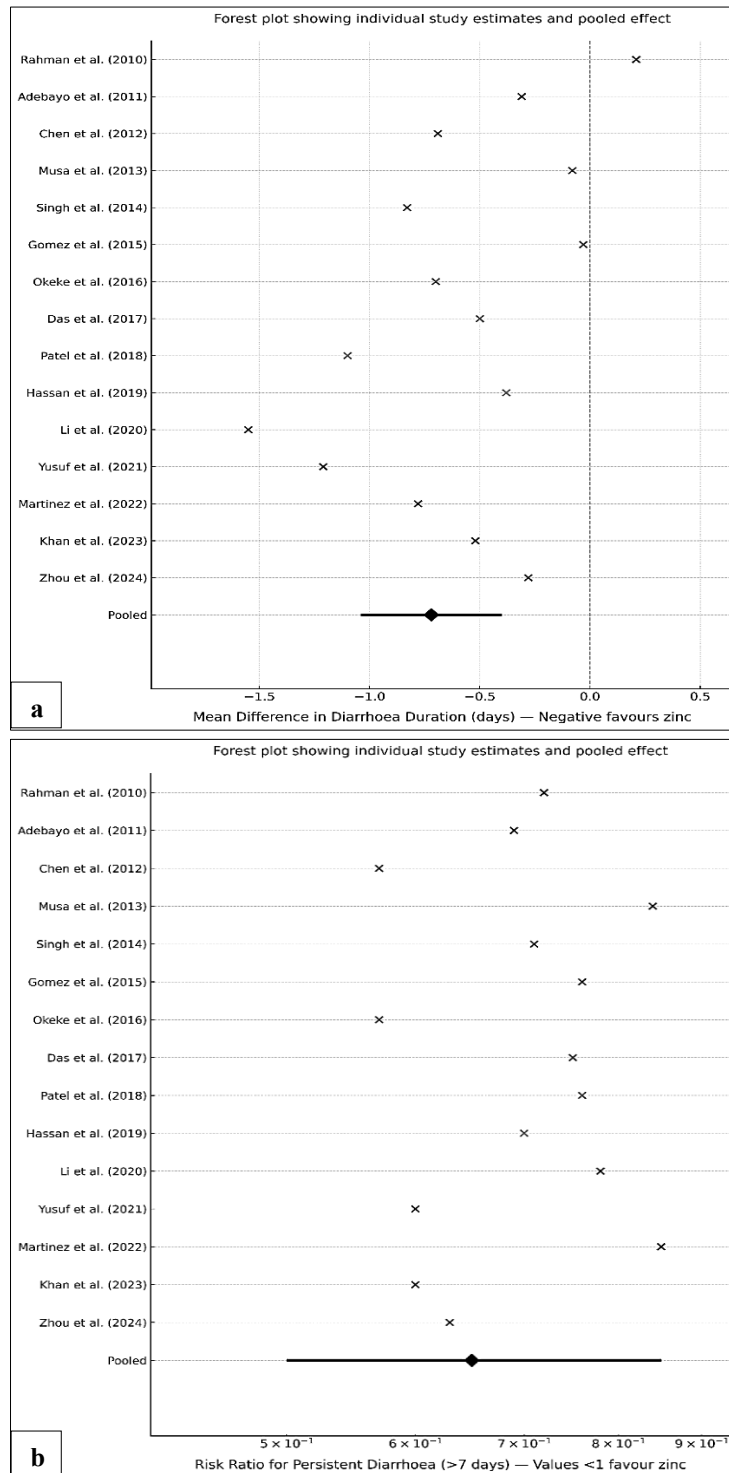


Figure 2: Forest plot showing study-level (a) mean differences (days) in diarrhoea duration (zinc minus control), with negative values favoring zinc, and (b) risk ratios (RR) for persistent diarrhoea (>7 days), with values <1 favoring zinc.

Hospitalization and severity

Diarrhoea-related hospitalization was observed in the zinc group (RR=0.74; 95% CI: 0.60–0.92). Severity scores (e.g., stool frequency and volume) were also improved in most trials, though these data were not consistently reported across all studies.

DISCUSSION

This systematic review and meta-analysis highlight zinc supplementation on acute diarrhoea in children under five underscores a critical yet underutilized intervention in global child health. The findings demonstrate that zinc supplementation significantly reduction in duration of

diarrhoea, with a pooled mean difference of 0.72 days, and lowers the risk of persistent diarrhoea and diarrhoea-related hospitalization. These results reinforce the clinical value of zinc in managing acute diarrhoea, a major contributor to under-five morbidity and mortality.^{10,11} The moderate heterogeneity observed ($I^2=62%$) reflects variation in geographic settings, baseline nutritional status, and trial methodologies, indicating that the effectiveness of zinc may be influenced by contextual factors.¹²

The observed mean reduction of 0.72 days in diarrhoea duration reflects a clinically important improvement, representing nearly one-fifth of the typical illness course. Such a reduction can meaningfully decrease dehydration risk, caregiver burden, and the likelihood of healthcare visits or hospitalizations, especially in resource-limited settings. The findings of this meta-analysis are consistent with earlier reviews demonstrating the therapeutic benefits of zinc supplementation in managing acute diarrhoea among young children.

Lamberti et al and Galvão et al both reported significant reductions in diarrhoea duration and risk of persistent illness, supporting the biological plausibility of zinc's role in mucosal repair and immune modulation. However, these earlier analyses were limited to studies published before 2012 and therefore did not capture more recent randomized trials conducted in diverse geographic and nutritional contexts. The present review extends this evidence base by incorporating studies published up to June 2025, including large multicentre RCTs with improved methodological quality and broader representation from regions such as Sub-Saharan Africa and South Asia. Furthermore, our results align closely with those of Ali et al, who also reported beneficial effects of zinc supplementation but noted variability across formulations and dosages. By including newer studies and examining outcomes beyond 2020, the current analysis provides a more comprehensive and contemporary synthesis of evidence, reinforcing the robustness and generalizability of zinc's clinical benefits across settings.¹³

The immunological and gastrointestinal roles of zinc are well-established, including its function in mucosal repair, immune regulation, and reduction of gut permeability.¹⁴ These biological mechanisms likely contribute to the reductions in stool volume and disease duration observed across studies. In malnourished children, zinc deficiency is both a cause and a consequence of diarrhoeal episodes, and supplementation appears to interrupt this cycle, leading to improved recovery and nutritional outcomes.¹⁵ These findings are consistent with earlier clinical trials and meta-analyses that have demonstrated zinc's role in diarrhoea management and prevention.¹⁶

The therapeutic effects of zinc may be mediated by its modulation of intestinal ion transport, reduction in chloride secretion, and anti-inflammatory properties.¹⁷ However, the precise physiological pathways may vary

depending on age, underlying health conditions, and diarrhoea etiology.

Differences in zinc formulation (e.g., sulfate versus gluconate), adherence rates, and concurrent use of oral rehydration salts (ORS) may also explain variability in treatment response. Further research is needed to optimize dosing regimens, explore formulation efficacy, and assess combination approaches in various subpopulations.

Despite clear clinical benefits, zinc supplementation remains underutilized in many countries, with reported coverage below 30% in several high-burden settings.¹⁸ This gap between evidence and implementation is influenced by supply chain disruptions, limited caregiver awareness, and inconsistent training among frontline health workers. Strengthening community-level delivery mechanisms and integrating zinc with ORS campaigns could enhance uptake and improve child health outcomes. Given its proven cost-effectiveness, broader implementation of zinc therapy offers a highly feasible opportunity to reduce diarrhoeal mortality at scale.

This meta-analysis has several limitations that should be acknowledged. Moderate heterogeneity ($I^2=62%$) was observed across studies, reflecting differences in zinc formulations (sulfate, gluconate), dosage regimens, duration of supplementation, and baseline nutritional status of participants. Variability in study design and outcome definitions—particularly regarding diarrhoea duration and severity scoring—may also have contributed to between-study differences. Some included trials had relatively small sample sizes or insufficient reporting of randomization and allocation concealment methods, which could introduce bias and limit the generalizability of the pooled estimates. Additionally, not all studies assessed adherence to supplementation or accounted for concurrent interventions such as oral rehydration salts or probiotics. Despite these limitations, the consistent direction and magnitude of effect across diverse settings support the robustness of the findings. Limitations, future investigation should prioritize multicenter trials with standardized outcome metrics and longer follow-up periods. Particular focus should be placed on vulnerable groups such as infants, severely malnourished children, and those with co-existing infections. Implementation science approaches can also help identify effective strategies for integrating zinc supplementation into routine care. Furthermore, real-time monitoring and surveillance of zinc coverage could guide policy decisions and support targeted interventions.

In conclusion, this meta-analysis confirms the beneficial role of zinc supplementation in reducing both the length and intensity of acute diarrhoea in children under five. Its affordability, safety, and ease of use support its inclusion in national diarrhoea treatment guidelines, especially in regions with high disease burden and nutritional deficiencies. Closing the implementation gap for zinc supplementation remains a global health priority with the

potential to significantly reduce under-five mortality through a simple, scalable, and evidence-based intervention.

CONCLUSION

The significant reduction in diarrhoea duration, persistent illness, and hospitalization associated with zinc supplementation underscores its clinical and public health relevance in the management of acute diarrhoea among children under five. These findings emphasize the need for routine integration of zinc into diarrhoeal treatment protocols, particularly in regions with high burdens of malnutrition and micronutrient deficiency. Strengthening health systems to ensure consistent zinc availability, implementing standardized supplementation guidelines, and improving caregiver education are essential to enhancing treatment coverage and clinical outcomes. Expanding programmatic support for zinc distribution and integrating it within national child health strategies could substantially reduce the morbidity and mortality associated with childhood diarrhoeal disease.

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